ARCHIVES of INTERNAL MEDICINE

VOLUME 60 NOVEMBER 1937 NUMBER 5

COPYRIGHT, 1937, BY THE AMERICAN MEDICAL ASSOCIATION

PNEUMONIA DUE TO BACILLUS FRIEDLÄNDERI

A REPORT ON FORTY-ONE PATIENTS, WITH CONSIDERATION OF SPECIFIC SERUM THERAPY

JESSE G. M. BULLOWA, M.D.
Clinical Professor of Medicine, New York University College of Medicine.

JOSEPH CHESS, M.D.
AND
NATHAN B. FRIEDMAN, M.D.
Residents, Service for Acute Disease of Respiratory Tract, the Harlem Hospital
NEW YORK

The existence of pulmonary disease attributable to Bacillus Friedländeri has been recognized for a number of years. Most of the previous reports have been based on isolated cases or small groups of cases, with two or three outbreaks approaching epidemic proportions. Examination of these reports reveals that they have been concerned with various features of the organism and the disease.

There have been extensive bacteriologic, cultural and immunologic studies of Friedländeri, with more recent work on their subdivision into several morphologically identical but serologically distinct groups. These have been further concerned with the etiologic significance of the presence of B. Friedländeri in diseased pulmonary tissue and its relative incidence in the pneumonias, in extrapulmonary diseases and in the carrier state.

Clinical study has distinguished the chronic form of the disease, which simulates pulmonary tuberculosis, from the acute fulminating form, with a uniformly high mortality rate, like that of pneumococcic lobar pneumonia. From a pathologic point of view, lobar, lobular, bronchopneumonic and mixed varieties have been noted, and a characteristic roentgenographic picture based on a corresponding pathologic concept has been described.

This study received support in part from the Metropolitan Life Insurance Company.

From the Littauer Pneumonia Research Fund, New York University; the Medical Service, the Harlem Hospital, and the Bureau of Laboratories, the Department of Health.

ETIOLOGY AND BACTERIOLOGY

The confusion in the early studies of Friedländer, Fraenkel and Weichselbaum regarding the various organisms found in pneumonic consolidations has been eliminated, and the knowledge has been adequately summarized and clarified in many of the later reports.[1] It is necessary to mention here only the original difficulties in distinguishing the diplococcus of pneumonia from B. Friedländeri, both of which were found in similarly consolidated lungs; the relegation by most observers of B. Friedländeri to the rôle of secondary invader and, finally, the recognition that this organism serves as the sole causative agent in a definite but relatively small proportion of pulmonary infections.

It is interesting, however, that even as late as 1933, Baehr, Shwartzman and Greenspan[2] looked on primary infection of the lung due to B. Friedländeri as extremely rare. They stated: "when encountered in pneumonic and other infections of the lung it is seldom the primary cause of infection. More commonly it is either a secondary invader, a contaminant, or has reached the lung from the intestinal tract, the liver, the bile passages, or the urinary tract, by the blood stream or by direction extension."

Considerable bacteriologic and immunologic study has defined the position of B. Friedländeri in relation to the colon-typhoid-enteric group of gram-negative bacilli. B. Friedländeri may be described as gram-negative encapsulated bacilli varying from short forms, resembling diplococci, to thin rods and thick forms. The organisms may occur singly, as diplobacilli, or in chains and sheets, and they grow readily on culture at room temperature, yielding large viscid colonies on plates and a slimy pellicle in broth.

The serologic classification of Julianelle[3] has distinguished the different strains involved in human and in animal infections. A classification of this type is vital to rational attempts at serum therapy. Julianelle recognized A, B and C types and an X group of unclassified strains.

---

1. (*a*) Sisson, W. R., and Thompson, C. B.: Friedländer Bacillus Pneumonia, with Report of Cases, Am. J. M. Sc. **150**:713 (Nov.) 1915. (*b*) Belk, W. P.: Pulmonary Infections by Friedländer's Bacillus, J. Infect. Dis. **38**:115 (Feb.) 1926. (*c*) Sweany, H. C.; Stadnichenko, A., and Henrichsen, K. J.: Multiple Pulmonary Abscesses Simulating Tuberculosis Caused by Friedländer's Bacillus, Arch. Int. Med. **47**:565 (April) 1931. (*d*) Fremmel, F.; Henrichsen, K. J., and Sweany, H. C.: Pulmonary Infections by Friedländer's Bacillus, Ann. Int. Med. **5**:886 (Jan.) 1932. (*e*) Olcott, C. T.: Pneumonia Due to Friedländer's Bacillus, Arch. Path. **16**:471 (Oct.) 1933.

2. Baehr, G.; Shwartzman, G., and Greenspan, E. B.: The Rôle of Bacillus Friedländer in Infection, Tr. A. Am. Physicians **48**:353, 1933.

3. Julianelle, L. A.: The Distribution of Friedländer's Bacilli of Different Types, J. Exper. Med. **52**:439 (Oct.) 1930.

This nomenclature was used by us in the identification of the organisms in our cases. Classifications on the basis of fermentation reactions were unsatisfactory and did not parallel serologic groupings.

Avery, Heidelberger and Goebel [4] demonstrated chemical as well as immunologic relationships between Pneumococcus type II and a strain of B. Friedländeri, later identified as B. Friedländeri of type B; and Goebel [5] called attention to the isomeric relationship between the aldobionic acids present in the specific soluble carbohydrates in the capsules of B. Friedländeri A and that of Pneumococcus type II, although he noted no immunologic resemblance.

INCIDENCE

The reported incidence of B. Friedländeri as the causative agent in pneumonia varies. In a series of 2,000 cases of pneumonia, Cecil, Baldwin and Larsen [6] found a 0.4 per cent incidence of pure infections, whereas Gay [7] said he believed the incidence to be as high as from 8 to 10 per cent in croupous and still higher in bronchopneumonic and mixed infections. Bhatnagar and Singh [8] recently reported 13 cases of pneumonia due to B. Friedländeri in a series of 100 cases of pneumonia in India. In a series of 3,768 cases of pneumonia among adults studied bacteriologically at the Harlem Hospital from 1929 to 1936, 41 instances of pneumonia due to B. Friedländeri were noted, comprising 1.1 per cent of the total number of cases.

In the upper portion of the so-called normal respiratory tract Bloomfield [9] found the bacillus in 5.8 per cent of 85 unselected cases, with the most frequent localization in the tonsils. In the carrier state Gay [7] mentioned it as existing in up to 25 per cent of normal human beings. Among 855 cases in which secretions of the respiratory tract were

4. Avery, O. T.; Heidelberger, M., and Goebel, W. F.: The Soluble Specific Substance of Friedländer's Bacillus: II. Chemical and Immunological Relationships of Pneumococcus Type II and of a Strain of Friedländer's Bacillus, J. Exper. Med. **42**:709 (Nov.) 1925.

5. Goebel, W. F.: The Soluble Specific Substance of Friedländer's Bacillus: IV. On the Nature of the Hydrolytic Products of the Specific Carbohydrate from Type A Friedländer Bacillus, J. Biol. Chem. **74**:619 (Sept.) 1927.

6. Cecil, R. L.; Baldwin, H. S., and Larsen, N. P.: Lobar Pneumonia: A Clinical and Bacteriologic Study of Two Thousand Typed Cases, Arch. Int. Med. **40**:253 (Sept.) 1927.

7. Gay, F. P., and others: Agents of Disease and Host Resistance, Springfield, Ill., Charles C. Thomas, Publisher, 1935.

8. Bhatnagar, S. S., and Singh, K.: Bacteriological Studies in Acute Lobar Pneumonia Due to Pneumococcus and B. Pneumoniæ Friedländer, Indian J. M. Research **23**:337 (Oct.) 1935.

9. Bloomfield, A. L.: The Mechanism of the Bacillus Carrier, with Special Reference to the Friedländer Bacillus, Am. Rev. Tuberc. **4**:847 (Jan.) 1921.

studied bacteriologically in the medical service at the Harlem Hospital (the patients were suffering chiefly from miscellaneous infections of the respiratory tract), B. Friedländeri was found in 19 (2.2 per cent). In 11 of these cases B. Friedländeri of type A was present. Pneumococci were found in 593 cases (69 per cent).

The organism has also been found in chronic pulmonary abscess, influenza, empyema and miscellaneous infections of the bronchial tree and larynx.

The pathogenicity of B. Friedländeri in man is not limited to the respiratory tract. The organism has been found to involve the gastrointestinal and genito-urinary tracts, and it frequently invades the blood stream as well.

Although most of the cases of pneumonia reported as due to B. Friedländeri were isolated instances or appeared in small groups, several outbreaks approaching epidemic proportions have been reported, the most prominent being the one cited by Zander [10] in 1919. He described several hundred cases of pneumonia due to B. Friedländeri occurring chiefly in patients below middle age. There was a mean duration of illness of nine and one-half days, and the mortality was approximately 29 per cent. Zander noted the occurrence of relapses and the tendency toward transition from the active to the carrier state. Kliewe [11] reported an epidemic of infections of the upper portion of the respiratory tract and of the lungs due to B. Friedländeri in 11 children who were exposed to a patient with pneumonia known to be due to B. Friedländeri. Jampolis, Howell, Calvin and Leventhal [12] reported an outbreak of gastroenteritis attributable to B. Friedländeri, several cases of which were complicated by invasion of the blood stream and pulmonary involvement. In the present study of 41 cases, a fairly even distribution over a seven year period was noted, except for November 1935. During that month there were 5 cases, all of which began within the span of a few days. Of these 5 cases, 4 were caused by B. Friedländeri A, and the fifth, by an unclassified B. Friedländeri (not an A). The appearance of 5 cases in one month, as contrasted with 41 cases distributed over a period of seven years, appears to be of epidemiologic significance.

---

10. Zander: Ausgedehnte Endemie von Lungenentzündungen durch Infektion mit Friedländerschen Pneumobazillen unter Zivilarbeiten, Deutsche med. Wchnschr. **45**:1180, 1919.

11. Kliewe, H.: Epidemiologische und biologische Studien über den B. pneumoniae Friedländer und verwandte Arten, Zentralbl. f. Bakt. (Abt. 1) **116**:92, 1930.

12. Jampolis, M.; Howell, K. M.; Calvin, J. K., and Leventhal, M. L.: Bacillus Mucosus Infection of the New-Born, Am. J. Dis. Child. **43**:70 (Jan.) 1932.

CLINICAL AND PATHOLOGIC STUDIES

Most observers in the past have described in detail the gross and microscopic observations in pulmonary consolidations caused by B. Friedländeri. Their descriptions are fairly consistent as regards the massive consolidation, the viscid exudate and the tissue necrosis which results in gross and microscopic abscesses, with and without cavitation. They have also recorded the marked cytolosis, the hemorrhage, the mononuclear and polymorphonuclear alveolar exudates and the widespread overgrowth of easily recognizable bacilli, with extensive phagocytosis. The interpretation of these features, however, varied considerably when attempts were made to classify the consolidation as lobar, lobular, confluent lobular or bronchopneumonic. Most observers hesitated to call the massive consolidation "lobar," preferring to designate it as lobular or confluent lobular.

A chronic remissive form, resembling and frequently mistaken for pulmonary tuberculosis, has been described. This variety followed the onset of acute pneumonia in the case described separately by Berglund [13] and Westermark [14] and persisted for nine years in the case reported by Brulé, Huguenin and Dreyfus.[15] The chronic form is characterized by remissions and exacerbations, with pulmonary cavitation, fibrosis and bronchiectasis. Sweany, Stadnichenko and Henrichsen [16] discussed the chronic aspect of the disease and the pathogenesis of infection of the lung due to B. Friedländeri as beginning with bacterial spread, mononuclear phagocytosis and hemorrhage, followed by polymorphonuclear infiltration, vascular engorgement, thrombosis and, finally, resolution with necrosis.

Reconstruction of the disease process was attempted by Kornblum and Collins [16] by means of repeated roentgenographic studies. They visualized four consecutive stages: (1) incipient bronchopneumonia, followed by (2) secondary pseudolobar confluence, which soon breaks down and results in (3) the formation of multiple thin-walled abscess cavities and goes on to (4) a stage of fibrosis and healing. They con-

13. Berglund, N.: Fall von Friedländerpneumonie unter dem Bilde einer Lungentuberkulose: Terminale Affektion der Harnwege, Beitr. z. Klin. d. Tuberk. **62**:745, 1925-1926.

14. Westermark, N.: Ein Tuberkulose vortäuschender Fall von Friedländer's Pneumonia mit lange sich hinziehendem Verlauf, Acta radiol. **7**:626, 1926.

15. Brulé, M.; Huguenin, R., and Gilbert-Dreyfus: Pneumopathie chronique à bacilles de Friedländer, Bull. et mém. Soc. méd. d. hôp. de Paris **51**:1370 (Oct.) 1927.

16. Kornblum, K.: The Roentgen-Ray Diagnosis of Pulmonary Infections with the Friedländer Bacillus, Am. J. Roentgenol. **19**:513 (June) 1928. Collins, J. H., Jr., and Kornblum, K.: Chronic Pulmonary Infection Due to Friedländer's Bacillus: A Clinical and Roentgenologic Study, Arch. Int. Med. **43**:351 (March) 1929.

TABLE 1.—*Data for Patients Not Receiving Serum*

Case No.	Initials	Color	Time of Illness	Sex	Age	Onset	Lobes Involved	Causative Organism*	Course	Duration of Illness, Days	Results of Blood Culture
1	N. T.	N	Oct. 1932	M	50	Infection of upper respiratory tract; chilliness	RUL RML RLL	BFA	Leukopenia; death	9	+
2	R. M.	W	Jan. 1933	M	73	?	LLL	BFB	Leukopenia; death	2(?)	+
3	D. D.	N	Jan. 1933	M	31	Typical pneumonic infection	RUL	BFA	Leukopenia; respiratory distress; death Necropsy: coarse granular red and gray hepatization of RUL and RML	2	+
4	H. I.	W	March 1933	M	62	Typical pneumonic infection	LUL LLL	BFA	Pulmonary edema; death	7	+
5	R. B.	N	April 1933	M	42	Infection of upper respiratory tract; typical pneumonia	RUL RML RLL	BFA	Pulmonary edema; death	3	—
6	R. M.	N	June 1933	M	47	Typical pneumonia; headache	RUL	BF	Leukopenia; peripheral vascular collapse; death	9	+
7	H. K.	W	June 1933	M	51	Alcoholic indulgence; submergence; typical pneumonia; no chill	RLL LLL	BFB	Leukopenia; pulmonary edema; hyperpyrexia; death	3	+
8	J. D.	W	Sept. 1935	M	43	Chronic cough; typical pneumonia	RLL	BF (not A)	Death	3	+
9	M. B.	N	Aug. 1935	M	51	Typical pneumonia; no chill	RUL RML RLL	BFA	Peripheral vascular collapse; death Necropsy: red granular hepatization of RUL, RML and RLL	6	+
10	T. J.	W	Nov. 1935	M	60	Typical pneumonia	RUL LLL	BF (not A)	Peripheral vascular collapse; death	3	+
11	R. J.	N	Nov. 1935	M	29	Infection of upper respiratory tract; typical pneumonia	LUL LLL	BFA	Leukopenia; delirium; death	4	+
12	P. J.	N	Nov. 1935	M	29	Typical pneumonia	RUL RML RLL	BFA	Leukopenia; death	2	+
13	B. G.	N	Nov. 1935	M	42	Alcoholic indulgence; cough; emesis	LUL	BFA	Leukopenia; distention; delirium; death	5	+
14	E. M.	N	Feb. 1931	M	36	? Cough; pain	RUL	BF	Herpes; cavitation; recovery	? wk.	—
15	L. P.	N	Feb. 1936	F	68	Typical pneumonia	LUL	BFA	Pulmonary edema; death	4	—
16	T. S.	W	Jan. 1934	M	65	Alcoholic indulgence; chronic cough; typical pneumonia	RLL LLL	BFA PV	Delirium; death	10	+

17	E. M.	N	Jan. 1934	F	37	Typical pneumonia	RLL	BFA	Delirium; hyperpyrexia; death	13	+
18	W. S.	N	Jan. 1934	M	70	Typical pneumonia	RLL	BF	Pulmonary edema; death Necropsy: gray hepatization of RLL	11	+
19	M. B.	N	Sept. 1934	F	32	Typical pneumonia; emesis	LUL	BF (not A)	Incontinence; delirium; hyperpyrexia; death	5	+
20	C. T.	N	Sept. 1934	M	43	Typical pneumonia; abdominal pain; diarrhea	RUL	BFA	Peripheral vascular collapse; death Necropsy; gray-yellow consolidation of RUL, with hemorrhage	6	—
21	L. M.	N	Nov. 1934	M	38	Infection of upper respiratory tract; thoracic pain; emesis	RUL	BFA	Leukopenia; peripheral vascular collapse; death	5	—
22	W. H.	N	Oct. 1934	M	42	Typical pneumonia	RML RLL	BFA	Death Necropsy: gray hepatization of RML and RLL, with abscess	6	+
23	W. J.	N	Nov. 1934	M	58	Typical pneumonia; diarrhea; emesis	RLL	BFA	Respiratory distress; death	3	—
24	J. A.	W	Jan. 1935	M	47	Typical pneumonia; hemoptysis; erythema	RUL	BFA	Peripheral vascular collapse; death	5	+
25	M. N.	N	June 1929	F	58	Exposure; typical pneumonia; no pain	RUL LLL	BF	Pulmonary edema; death	6	+
26	M. B.	N	Jan. 1930	M	49	Thoracic trauma; typical pneumonia; emesis; hemoptysis	RLL	BF	Leukopenia; death	3	+
27	A. W.	N	May 1931	F	31	Typical pneumonia	RLL LLL	BFD	Delirium; death Necropsy; grayish pink consolidation of LLL, with abscess and bronchial necrosis; similar patch in RLL	12	+
28	I. B.	N	May 1931	M	51	Alcoholic indulgence; typical pneumonia; no chill	RLL	BF	Diarrhea; death Necropsy: gray hepatization of RLL and RML and half of RUL; red hepatization of RML	5	+
29	J. T.	N	Jan. 1932	M	59	Typical pneumonia; no chill; emesis	LLL	BFA	Delirium; death	3	—
30	R. L.	N	Sept. 1931	M	77	Typical pneumonia; no chill	LLL	BF	Leukopenia; pulmonary edema; death Necropsy: gray hepatization of LLL	?1	+
31	J. H.	N	March 1932	M	48	Coma	RUL RML RLL	BF (not A)	Respiratory distress; peripheral vascular collapse; death	?2	—
32	C. W.	N	Sept. 1935	M	57	Typical pneumonia; no chill	RUL	BFA	Recovery	10	—
33	J. J.	N	July 1935	M	41	Typical pneumonia; delirium	RUL RML RLL	BFC	Diarrhea; melena; recovery	11	+

* BF indicates B. Friedländeri, the type (A, B, C, or D) being designated when known. PV indicates Pneumococcus type V.

sidered, as did Hart,[17] that the roentgenographic picture of multiple thin-walled cavities was characteristic of the disease. Collins made a follow-up study in several cases for from two to seven years, and in his recent survey [18] he reemphasized the resemblance to chronic pulmonary tuberculosis.

French writers [19] have classified the various types of involvement as follows: (1) the *hyperacute* or *superacute* type, characterized by overwhelming toxicity, massive consolidation and an almost invariably fatal termination; (2) the *acute* type, characterized by hepatization, with abscess formation, and occasionally by recovery, and (3) the *subacute* or *subacute suppurative pneumonic* type, in which the patient survives the acute stage and experiences an extended period of remission and exacerbation, ultimately showing clinical and roentgenographic evidence of cavitation.

Pathologically, they classified the lesions into the lobar group, the bronchopneumonic group and the pseudopneumonic group, the last being considered typical of infection due to B. Friedländeri. They expressed doubt that B. Friedländeri alone could give rise to a purely lobar distribution without the presence of a primary or of an associated pneumococcic invader.

The strikingly fulminating clinical course of acute pneumonia due to B. Friedländeri as well as the uniformly high mortality has been well recognized by most observers, and, except for minor individual variations, their findings agree in essence with ours, which will now be described in detail.

REPORT OF CASES

Forty-one patients (tables 1 and 2) with pneumonia due to B. Friedländeri were studied at the Harlem Hospital during the seven year period from June 1929 to June 1936. The diagnosis of pneumonia in each case was made by clinical and roentgenographic study, and B. Friedländeri was recovered either from the blood or from the material obtained by pulmonary suction or from both, as well as from the sputum.

---

17. Hart, A. L.: The Postpneumonic Lung: A Critical Review, Am. J. Roentgenol. **26**:371 (Sept.) 1931.

18. Collins, L. H., Jr.: Chronic Pulmonary Infection Due to the Friedländer Bacillus: Further Observations, Arch. Int. Med. **58**:235 (Aug.) 1936.

19. Macaigne, M.: Maladies infectieuses, in Roger, G. E. H.; Widal, F., and Teissier, P. J.: Nouveau traité de médecine et de thérapeutique, Paris, Masson & Cie, 1920. Letulle, M., and Bezançon, F.: La pneumonie disséquante necrotique, Ann. de méd. **12**:1 (July) 1922. Lemierre, A., and Levesque, J.: Les pneumopathies à pneumobacilles de Friedländer, Arch. méd.-chir. de l'app. respir. **2**:97 (April) 1927. Stoichita, N. N., and Jonnesco, D.: Abcès du poumon et septicémie à pneumobacilles de Friedländer, ibid. **8**:534, 1933.

TABLE 2.—*Data for Patients Receiving Serum*

Case No.	Initials	Color	Time of Illness	Sex	Age	Onset	Lobes Involved	Causative Organism	Course	Duration of Illness, Days	Results of Blood Culture
1	L. B.	N	April 1931	M	28	Typical pneumonia; emesis; arthritis	RLL	BF	Herpes; epistaxis; delirium; recovery	6	+
2	L. O.	W	May 1932	M	45	Typical pneumonia; emesis	RUL	BFA	Leukopenia; meningeal involvement; delirium; hyperpyrexia; death	10	+
3	J. W.	N	Nov. 1932	M	36	Typical pneumonia; no chill	LLL	BFA	Recovery	8	—
4	J. W. (case 3)	N	Jan. 1935	M	38	Typical pneumonia	RUL	BFA	Distention; delirium; peripheral vascular collapse; death Necropsy: gray granular consolidation of RUL; adhesions of left lung	4	—
5	E. S.	W	Nov. 1935	M	53	Typical pneumonia	RUL	BFA	Erythema; leukopenia; peripheral vascular collapse; death	4	—
6	E. T.	W	Oct. 1935	M	52	Thoracic trauma; infection of upper respiratory tract; typical pneumonia	RUL	BFA	Leukopenia; delirium; recovery	12	—
7	J. W.	N	Aug. 1932	M	26	Typical pneumonia	RLL	BFA	Recovery; serum sickness	7	—
8A	A. M.	N	May 1936	M	43	Typical pneumonia	RLL	BF (not A)	Delirium; death Necropsy: gray hepatization of RLL	1	+

In view of the reported high incidence of B. Friedländeri in the carrier state, 4 patients, 3 of whom died, who presented positive findings only in the sputum were not included in this series.

The organisms were identified and typed and are shown classified into serologic groups in table 3. Swelling of the capsule took place with the homologous antiserum as it occurs with the pneumococcus under similar conditions. Pulmonary suction was performed in all cases as soon as the presence of consolidation was established. The positive results of growth of material obtained by pulmonary suction during life in the presence of positive results of blood culture is, of course, of doubtful significance, since some blood may be aspirated through the needle. However, positive results of pulmonary suction confirming the sputum findings were obtained for 19 patients at the time the blood cultures were sterile. In one instance a typical viscid exudate was aspirated, while in another direct smear of the material aspirated revealed the presence of numerous Friedländer bacilli.

TABLE 3.—*Distribution of Cases According to Type of Infecting Organism, Bacteremia and Mortality* *

Type of B. Friedländeri	Total No. of Cases	Deaths		Recoveries	
		Total	Bacteremia	Total	Bacteremia
A	24	20	(12)	4	(0)
B	2	2	(2)	0	0
C	1	0	0	1	(1)
Untyped (not A)*	6	6	(5)	0	0
Untyped	8	6	(6)	2	(1)
	41	34	(25)	7	(2)

* Tested only for type A.

The distribution of the 41 cases over the seven year period is shown in figure 1. In the entire group there were 36 (or 88 per cent) men, 10 of whom were white and 26, Negroes. All 5 women were Negresses. The distribution by age is shown in figure 2.

Such predisposing factors as alcoholism, trauma, submergence and chronic nontuberculous pulmonary disease were present only occasionally. Twenty-one, or approximately half, of our patients contracted the disease with the suddenness characteristic of pneumococcic lobar pneumonia and presented the typical chill, pleural pain and cough productive of blood-stained sputum. Profound and rapidly progressive prostration was characteristic. The physical signs of consolidation were commonly classic, but occasionally a patient presented practically no physical signs, in spite of the most extensive involvement revealed by the roentgenogram or by the postmortem examination. Coarse moist râles were frequently noted.

In two thirds of the patients the sputum did not differ grossly from that seen in pneumococcic lobar pneumonia, being either blood-tinged or rusty. The remaining third, however, showed sputum which has been frequently described as typical of pneumonia due to B. Friedländeri, being thick, gelatinous and diffusely bloody. It was expectorated copiously but with difficulty, adhering to the lips of the patient and to the sputum cup. Some of the patients had free hemoptysis; others occasionally expectorated a thin sputum resembling currant jelly.

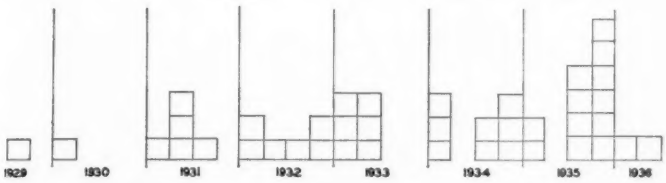


Fig. 1.—Distribution of pneumonia due to Friedländer's bacillus. Each square represents 1 case.

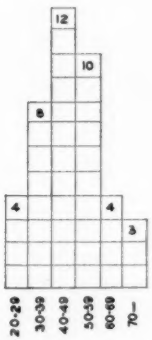


Fig. 2.—Distribution of pneumonia due to Friedländer's bacillus according to the ages of the patients.

Microscopically, the sputum was usually found to be teeming with gram-negative encapsulated bacilli, varying in thickness and in length and lying singly, in short chains or as diplobacilli.

The distribution of the consolidation was usually purely lobar, although not infrequently the process extended beyond the interlobar fissure and involved the adjacent pulmonary tissue. Isolated patches were occasionally noted on the same or on the opposite side. In a few patients diffuse and irregular involvement was noted, as in one patient in whom submergence was a predisposing factor. The distribution by lobes is given in figure 3. In 32 of the 41 patients there was complete

or partial involvement of the right lung, as contrasted with involvement of the left side in 14 patients. One of the 6 patients with complete consolidation of the right lung recovered; not any of the 5 patients with bilateral involvement recovered.

The course of the illness was not marked by any unusual preponderance of extrapulmonary manifestations. Ten patients had associated gastro-enteritis, with vomiting and diarrhea, and in 1 instance melena was present. Two patients presented extensive erythemas, 1 of which was scarlatiniform. Three patients manifested delirium early,

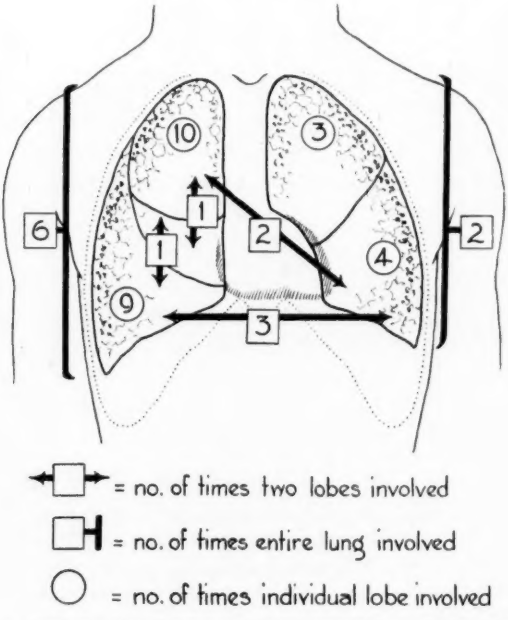


Fig. 3.—Distribution of the pneumonic consolidation in 41 patients.

but headache was prominent in only 1 patient. Six patients showed clinical, bacteriologic or pathologic evidence of meningeal involvement, and in only 1 of these did it occur in the absence of positive results of blood culture. No meningeal involvement was observed in the patients treated with serum or in those who recovered without serum treatment. Herpes occurred twice and epistaxis once; a nonsuppurative polyarthritis was noted in 1 patient.

Characteristic of the clinical course was the rapid dissolution. Fremmel, Henrichsen and Sweany [1d] reported on a patient who showed

typical involvement, with death occurring twenty-six hours after the onset. The shortest duration observed by us was thirty hours, and the average duration from onset to death was five and one-half days, with three fourths of the patients living six days or less. This may be compared with the findings for patients with lobar pneumonia due to Pneumococcus type II observed by us during a similar period for whom the average duration from onset to death was nine days.

The mode of termination varied. Nine patients died in peripheral vascular collapse, 7 of pulmonary edema and 3 of extreme respiratory

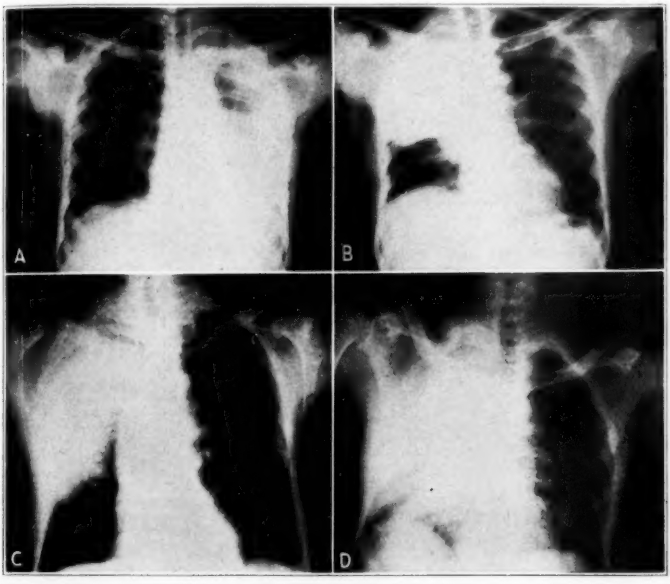


Fig. 4.—*A*, J. W. (table 2, case 3), a man aged 36, had a typical pneumonic invasion which lasted for eight days. The infection, due to B. Friedländeri A, involved the lower lobe of the left lung. Serum treatment was given. *B*, the same patient when 39 years old had a typical pneumonic invasion, with distention, delirium and peripheral vascular collapse. B. Friedländeri A was the cause of the infection. The upper lobe of the right lung showed gray granular consolidation, and there was pleural adhesion in the left lung. Death occurred on the fourth day. *C*, E. S. (table 2, case 5), a man aged 53, had a typical pneumonic invasion of the upper lobe of the right lung, with erythematous eruption, leukopenia and peripheral vascular collapse. Death occurred on the fourth day in spite of serum therapy. B. Friedländeri A was the cause of the involvement. *D*, R. M. (table 1, case 6), a man aged 47, showed typical pneumonic invasion of the upper lobe of the right lung, with headache, leukopenia and peripheral vascular collapse. Death occurred on the ninth day. Bacteremia was present, Friedländer's bacillus being recovered. Serum treatment was not given.

distress without pulmonary edema. Ten were in delirium, 2 showed uncontrollable distention and 1 was incontinent terminally. Four showed terminal hyperpyrexia, and relatively trivial procedures, such as venipuncture for blood culture, preceded death in a few instances.

The blood count showed conditions which varied between polymorphonuclear leukocytosis and the frequently described leukopenia. The latter was found in 14, or approximately one third, of our patients and was occasionally marked by an extreme preponderance of immature forms. The urine showed the usual changes found in febrile states. The curves for temperature and pulse and respiratory rates did not differ

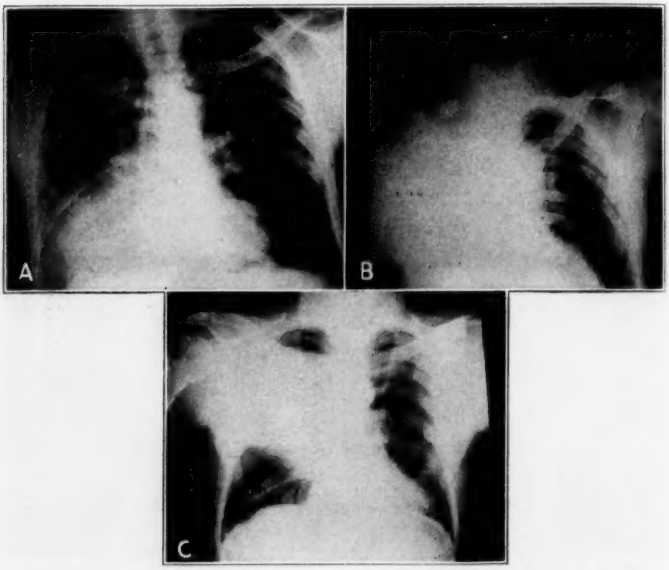


Fig. 5.—*A*, A. M. (table 2, case 8), a Negro aged 43, had a typical pneumonic infection with Friedländer's bacillus (not A) of the lower lobe of the right lung. The patient was delirious and died during the first day of illness. Necropsy revealed gray hepatization. *B*, M. B. (table 1, case 9), a man aged 51, had a typical pneumonic invasion without chill but with peripheral vascular collapse. Death occurred on the sixth day. Bacteremia was present, B. Friedländeri A being recovered. All three lobes of the right lung were involved. *C*, C. T. (table 1, case 20), a man aged 43, had a typical pneumonic invasion, with abdominal pain, diarrhea and peripheral vascular collapse. Death occurred on the sixth day. B. Friedländeri A was the cause of the infection of the upper lobe of the right lung.

significantly from those of pneumococcic lobar pneumonia. The temperature curves varied from sustained elevations to spiking, low or markedly irregular varieties. No single type seemed to predominate.

Roentgenographic studies of the chest showed the predominant finding to be a massive, dense, usually homogeneous shadow which was frequently suggestive of fluid. We were able to study 6 patients within forty-eight hours of onset, and in only 1 of them did we see the mottled roentgenographic appearance which Kornblum and others described as characteristic and from which they drew their conception as to the bronchopneumonic nature of the disease.

Thirty-four, or 83 per cent, of the entire group of patients died. Twenty-seven, or 66 per cent, showed positive results of blood culture either during the course of the illness or terminally; 25, or 93 per cent, of these patients died. One patient (T. S.) showed B. Friedländeri A and Pneumococcus type V repeatedly on pulmonary suction and blood culture and must be considered as showing a true mixed infection.

The available data obtained from a study of the agglutinins of the blood did not permit any definite conclusions to be drawn.

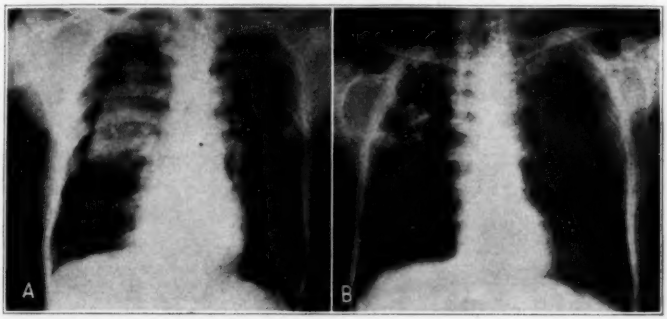


Fig. 6.—C. W. (table 1, case 32), a man aged 57, had a typical pneumonic invasion without a chill. B. Friedländeri A was the causative agent. The patient was febrile for eleven days. Recovery followed. *A*, the involvement of the upper lobe of the right lung, with pneumothorax induced by pulmonary suction; *B*, the residual cavitation.

In the 10 patients who came to necropsy (performed by Dr. S. Weintraub, pathologist) the predominant lesion was a massive lobar consolidation, the gray-yellow granular lung containing a viscid gelatinous exudate. Red hepatization was seen on 3 occasions, and abscess formation in the consolidated areas was noted twice. The abscess consisted of soft liquefied areas without pyogenic or cell-reactive membranes. Similar aputrid necroses were noted by us as well as by others in pneumococcic lobar pneumonia, particularly in pneumonia caused by Pneumococcus type III. Kessel [20] described similar obser-

20. Kessel, L.: The Clinical Aspect of Aputrid Pulmonary Necrosis, Arch. Int. Med. **45**:401 (March) 1930.

vations in 2 patients with lobar pneumonia due to Pneumococcus type II. Subpleural and intrapulmonary bleeding and fibrinopurulent pleuritis were also observed. The patients who recovered and who were followed up with roentgenographic examinations showed thickened pleurae or fibrosis, and in 1 patient excavation of the upper lobe of the right lung was noted. Microscopic studies of pulmonary tissue were

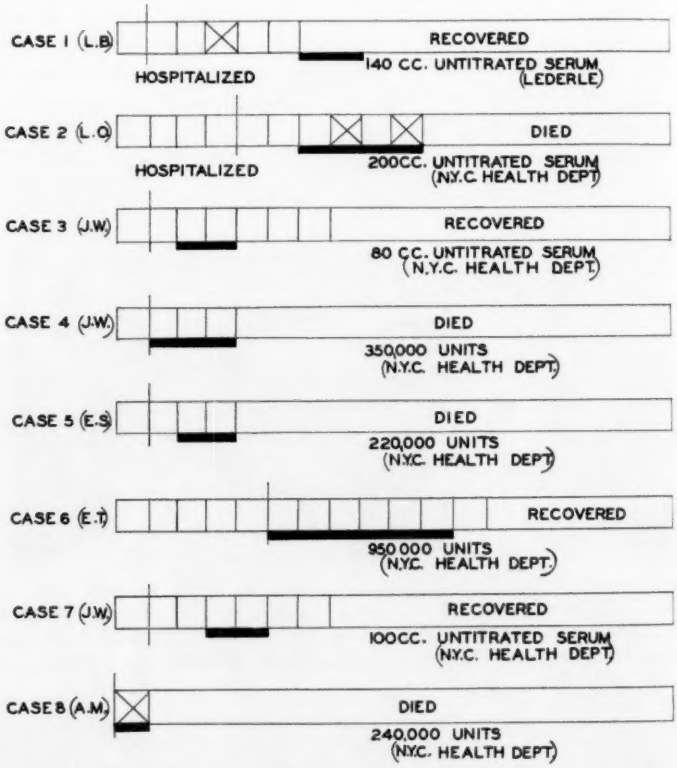


Fig. 7.—Serum treatment of patients with pneumonia due to Friedländer's bacillus (Klebsiella pneumoniae). Each square represents one day of illness. Crosses indicate positive results of blood culture.

in accord with those reported by other observers. The predominance of mononuclear alveolar exudates was noted, but polymorphonuclear infiltration was observed in 1 patient and granular edema in another.

Serum Therapy.—Specific serum therapy with B. Friedländeri A antiserum was attempted by us for 8 patients (table 2 and figure 4).

L. B. (table 2, case 1) was infected with an untyped B. Friedländeri and, in addition, received B. Friedländeri A antiserum after clinical recovery had already begun. Hence, this will not be considered as recovery due to serum treatment. L. O. (case 2) was given serum on the seventh day of illness. Death occurred on the eleventh day. J. W. (case 3) had pneumonia due to B. Friedländeri A which was limited to the lower lobe of the left lung. Serum was given on the third day, and recovery followed. The patient returned to the hospital twenty-six months later (case 4) with pneumonia due to B. Friedländeri A in the upper lobe of the right lung and died in spite of vigorous serum therapy instituted on the second day. At necropsy there were no parenchymal residua in the lung which had been involved twenty-six months previously. E. S. (case 5) entered with complete consolidation of the right lung, received serum on the third day and died in pulmonary edema. E. T. (case 6) had consolidation of the upper lobe of the right lung associated with leukopenia and complicated by delirium. He received serum on the sixth day and recovered. J. W. (case 7) received serum on the fourth day; recovery was complicated by serum sickness. A. M. (case 8) received B. Friedländeri A serum on the first day and died. He was found to be infected with an unclassified strain of B. Friedländeri which was not of type A. His death will be considered as occurring without serum treatment as the serum given was not specifically related to the infecting organism.

Omitting L. B. and A. M. (cases 1 and 8) from the group of patients treated, there were 6 patients treated with specific serum and 35 not so treated. Thirty (or 89 per cent) of the 35 patients who were not given serum died. Of these, 18 had infections due to B. Friedländeri A, and 17 (or 94 per cent) died. In 10 of these there was bacteremia, and in the 1 patient with pneumonia due to B. Friedländeri type A who recovered without the use of serum the blood culture was persistently sterile. Three (or 50 per cent) of the 6 with infections due to B. Friedländeri A who received specific serum therapy succumbed. The blood of the 3 who recovered was not invaded.

Although pneumonia due to B. Friedländeri is not commonly encountered, its fulminating course and high mortality present therapeutic difficulties and opportunities. While the patients treated by us with specific serum are far too few to permit the drawing of definite conclusions as to the value of serotherapy, the absence of other adequate therapeutic agents and the success which has attended serum therapy in related conditions warrant further attempts in this direction. Because of the fulminating character of the disease and the recognition that serum therapy, if it is to be at all effective, must be administered as early as possible, it is suggested that for every patient with lobar pneumonia who appears toxic out of proportion to the pulmonary

involvement and whose sputum suggests grossly the appearance described, a microscopic examination of sputum by direct smear be made at once. If the easily recognizable B. Friedländeri is found and can be typed, specific serum therapy should be instituted.

SUMMARY

A report on 41 patients with acute pneumonia due to B. Friedländeri is presented in an attempt to portray the disease as a clinical and pathologic entity. The findings for these patients showed a marked similarity to those for patients with pneumococcic lobar pneumonia.

The mortality rate for the entire group of 41 patients was 83 per cent. The highest mortality rate (94 per cent) occurred in patients infected with B. Friedländeri A who were not given serum.

Serum therapy was attempted for 8 of the patients, but in only 6 of them was the serum specifically related to the infecting organism. The mortality rate for these 6 patients who were infected with B. Friedländeri A and who received serum was 50 per cent, as contrasted with a mortality rate of 94 per cent for the 18 patients infected with the same organism and not treated with serum.

NOTE.—Since the preparation of our report Solomon [21] has published reports of 5 patients from Bellevue Hospital. Only 1 patient was treated as early as the third day. The 4 others were treated on the fifth day or later. The amount of serum given was inadequate. All his patients who received serum died.

21. Solomon, Saul: Primary Friedländer Pneumonia, J. A. M. A. **108**:937 (March 20) 1937.

HYPERINSULINISM

FINAL REPORT OF CASE INCLUDING NECROPSY OBSERVATIONS

EUGENE ZISKIND, M.D.

WALTER BAYLEY, M.D.

AND

EDGAR F. MAUER, M.D.

LOS ANGELES, CALIF.

The primary purpose of this paper is to record the subsequent progress and necropsy observations in the case of hyperinsulinism previously reported on.[1] In addition, mention will be made of special studies in regard to the phosphate content of the blood, psychomotor tests and the sugar content and pressure of the spinal fluid.

REPORT OF CASE

A short résumé of the previous report is presented:

A youth aged 19 was admitted in a state of coma to the Los Angeles County General Hospital on Sept. 8, 1930. For eighteen months he had had spells of weakness, headache, trembling and mental confusion which occurred at about noon. The sugar content of the blood was found to be 40 mg. per hundred cubic centimeters. He remained in coma for ten days. Right hemiparesis, anomial aphasia and apraxia and right hemianopia were present. The hemiparesis disappeared after three weeks; the aphasia, at the end of six weeks, and the hemianopsia, in ten weeks. Subsequent to the withholding of food the patient had a whole train of hypoglycemic symptoms associated with a fall in the sugar content of the blood, on one occasion as low as 28 mg. per hundred cubic centimeters. Abdominal exploration of the pancreas by one of us (W. B.) on March 26, 1931, revealed no abnormalities. Part of the tail and body of this organ were removed. The tissue was found to be entirely normal. The clinical course of the disease was unaltered.

Subsequent Clinical Course.—Between October 1931 and March 1932 the patient was under the care of Dr. Howard West. During that time attempts were made to control the hypoglycemia by means of a diet high in fat and low in carbohydrate, but this proved unsatisfactory. A second operation was performed by one of us (W. B.) on Jan. 26, 1933, and 22 Gm. of the body of the pancreas was removed. No abnormality was detected in the tissue, and again no change in the clinical course was observed.

From the Department of Neurology and the Department of Surgery, the School of Medicine of the University of Southern California, the Department of Pathology, the Los Angeles County Hospital, and the Department of Pathology, the College of Medical Evangelists.

1. Ziskind, E.: Hyperinsulinism: Report of a Case of Spontaneous Hypoglycemia, with Studies in Dextrose Tolerance, Arch. Int. Med. **52**:76 (July) 1933.

Further efforts with medicinal remedies were made. Ephedrine, ⅜ to ¾ grain (25 to 50 mg.) three times a day over a period of two weeks, was ineffective in producing any substantial change in the sugar level of the blood. It was previously shown that epinephrine constantly produced a rise in the sugar content of blood in this patient. Strom-Olsen [2] has demonstrated an increase and prolongation of the elevation of the sugar content of the blood in the dextrose tolerance test when epinephrine is administered simultaneously. In the hope of diminishing the number of feedings, epinephrine, 5 minims (0.3 cc.) four times a day for five days and 10 minims (6 cc.) four times a day for ten days, was administered subcutaneously, but the patient had just as many spells as before. As adrenal cortex extract has been reported to elevate the sugar content of the blood,[3] 2 cc. of a commercial extract of adrenal cortex [4] was given by hypodermic injection, but it caused no rise in the sugar content, and 1 cc. doses twice daily for ten days produced no salutary effects. Larger doses were not available because of the expensiveness of this medicine.

A preparation of the anterior lobe of the hypophysis,[5] 2 cc. by hypodermic injection, was given three times a week between October 3 and November 21 without materially affecting the sugar content of the blood. Wilder [6] previously recorded improvement in a case of hypoglycemia by treatment with a product of the anterior lobe of the pituitary gland.

Sodium dinitrophenol is said to produce a loss of weight, a rise in the sugar content of the blood and depletion of the glycogen stores.[7] Since the patient's weight had gradually increased in three years from 120 to 250 pounds (54.5 to 113.5 Kg.), any method to prevent a further increase in weight, particularly when associated with a rise in the sugar content of the blood and a depletion of the glycogen stores, appeared desirable. Sodium dinitrophenol was given in doses of 1½ to 4½ grains (97 to 292 mg.) during most of January and on through September 1934. On one occasion (February 19 to 21) the temperature rose to 40.9 C. (105.6 F.) rectally. Discontinuation of the medicine immediately resulted in a return of the temperature to normal. It was possible to renew the doses at the previous level without untoward symptoms, except for the appearance of a cutaneous rash on July 31 and September 25. The rash disappeared in both instances after the cessation of treatment. The drug was discontinued after the second appearance of the rash. During the nine months of treatment with dinitrophenol the patient gained only 6 pounds (3 Kg.). This represented a definite retardation of his previously rapidly increasing obesity. It is difficult to say whether or not the hypoglycemic manifestations were at all affected by the therapy.

---

2. Strom-Olsen, R.: The Blood Sugar Curve in Mental Cases, Lancet **1**:128 (Jan. 16) 1932.

3. Britton, S. W., and Silvet, H.: Effects of Cortico-Adrenal Extract on Carbohydrate Metabolism in Normal Animals, Am. J. Physiol. **100**:693 (May) 1932.

4. The preparation used was eschatin.

5. The preparation used was antuitrin.

6. Wilder, J.: Ein neues hypophysäres Krankheitbild: Die hypophysäre Spontanhypoglykämie, Deutsche Ztschr. f. Nervenh. **112**:192, 1930.

7. Hall, V. E.; Field, J., II; Sahyun, M.; Cutting, W. C., and Tainter, M. L.: Carbohydrate Metabolism, Respiration and Circulation in Animals with Basal Metabolism Heightened with Dinitrophenol. Am. J. Physiol. **106**:432 (Nov.) 1933.

The effect of the drug in this connection appears to us to warrant its further trial in other cases.

Throughout this entire period the patient had numerous hypoglycemic episodes. He had learned what the early prodromal symptoms were and would immediately take orange juice or some other carbohydrate. Control of the hypoglycemia in this manner proved more adequate than any method we could devise. During the night he rarely exceeded the three hour interval without food before hypoglycemic symptoms became apparent.

On Nov. 9, 1934, the patient appeared to be as well as usual and conversed normally with the nurse at 11:45 p. m. Ten minutes later he was found dead in bed, lying with his face buried in the pillow and his left arm reaching out for a bottle of orange juice on a nearby table. He was markedly cyanotic and was thought to have smothered in a hypoglycemic attack.

Gross Postmortem Observations.—The essential observations at necropsy, performed two hours after death, were as follows: The body was that of a markedly obese man about 25 years of age. The head and neck were extremely cyanotic.

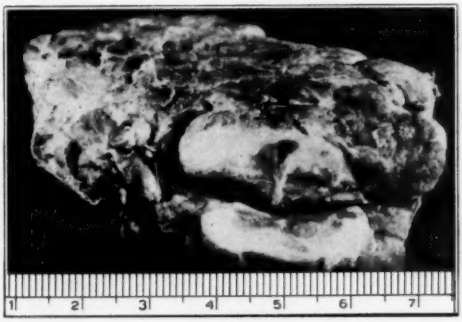


Fig. 1.—Remaining pancreas, showing section through the tumor.

The pupils were round, dilated and equal. There were several well healed surgical scars in the wall of the upper portion of the abdomen. The abdominal panniculus averaged 8 cm. in thickness.

The pancreas presented the major pathologic picture. Only the head and a portion of the body of the pancreas remained. It measured 8 by 5 by 2.5 cm. and weighed 50 Gm. Its appearance and consistency were normal except for an ovoid mass situated in the posterior surface of the distal portion of the body. The tumor measured 2.5 by 2 by 2 cm. (fig. 1). Its external surface consisted of gray-white fibrous material which formed an incomplete capsule and sharply demarcated the mass from the pancreatic parenchyma in approximately three fourths of its surface. The remaining portion was in contact with the surrounding pancreatic tissue but did not appear to invade it. On section the capsule of the tumor measured 2 to 3 mm. in thickness. The central portion of the tumor was pink-gray, firm and infiltrated by dense strands of connecitve tissue which appeared to be growing in from the capsule.

The thymus measured 5 by 3 by 2 cm. and was beefy red and soft. The testes and the pituitary, thyroid and parathyroid glands were normal, as were the adrenal glands, although the latter were somewhat increased in size. The brain was of

average size for an adult. The dura was normal. There were moderate pial injection and milky thickening of the leptomeninges over the anterior portion of the hemispheres. The brain surfaces were markedly cyanotic. The cerebellar tonsils showed a slight degree of herniation, and the uncinate gyri showed minor grooving; but there was no flattening of the cerebral convolutions. The blood vessels at the base of the brain were soft and thin walled. Coronal sections revealed symmetrical ventricles which were not dilated. The brain stem and cerebellum were without morbid change.

The heart weighed 380 Gm. There were numerous small petechial hemorrhages in the parietal pericardium. The left ventricular wall averaged 2 cm. in thickness. The aorta was hypoplastic. The diaphragm was at the level of the third rib on the right and the fourth rib on the left. The pleural surfaces were thin and glistening and contained a few small petechial hemorrhages. The trachea and bronchi were filled with bloody mucous material. The right lung weighed 475 Gm. and was grossly normal except for moderate hyperemia in its basal portions. The left lung weighed 425 Gm. and was similar in appearance.

The peritoneum was smooth and moist. The omentum was large; it contained a great deal of fat and was adherent to the anterior parietal peritoneum. The stomach contained a moderate amount of partially digested food. The small intestine was filled with yellow chyme. The solitary and agminate lymph follicles of the small and large intestines were hyperplastic. The liver weighed 3,300 Gm. The external and cut surfaces were smooth and pale yellow to brown. The lobules were not clearly demarcated; the central portions appeared pale yellow. The gallbladder, biliary passages and portal system were normal. The spleen was firm and weighed 340 Gm. On section it presented an acutely congested deep purple-red surface in which numerous closely packed hyperplastic malpighian corpuscles were seen. The kidneys together weighed 425 Gm. The capsules stripped readily from smooth, extremely cyanotic cortical surfaces. On section the renal architecture appeared normal, but the entire parenchyma was intensely cyanotic. The renal pelves, ureters, bladder, prostate and external genitalia were normal. The skeletal system presented no abnormality.

Histopathologic Observations.—The pancreatic parenchyma, except for the tumor, showed no microscopic abnormality. The islets appeared normal in size and number. The tissue immediately adjacent to the tumor, aside from slight compression, revealed no significant change. There was no evidence of infiltration by tumor cells (fig. 2*A*).

The capsule of the tumor consisted of dense collagenous connective tissue from which heavy strands projected into the central portions. One of these divided the mass into two unequal parts. Finer projections produced irregular lobulation (fig. 2*B*).

The capsule was infiltrated by slender irregular strands and large sheets of cells similar to those of which the tumor mass was composed. These will be described presently (fig. 3*A*).

Ducts of various sizes also were seen in the capsule. Some of them were markedly dilated, as though obstructed; others appeared compressed. In one area the duct epithelium appeared continuous with the tumor tissue (fig. 3*B*).

Bensley, studying the material of Womack and his associates,[8] worked out the various stages of islet cell tumors, using as criteria the vascular accommodation

8. Womack, N. A.; Gnagi, W. B., and Graham, Evarts A.: Adenoma of the Islands of Langerhans with Hypoglycemia, J. A. M. A. **97**:831 (Sept. 19) 1931.

Fig. 2.—*A*, the capsule with adjacent pancreas; *B*, the tumor adjacent to the capsule (× 65).

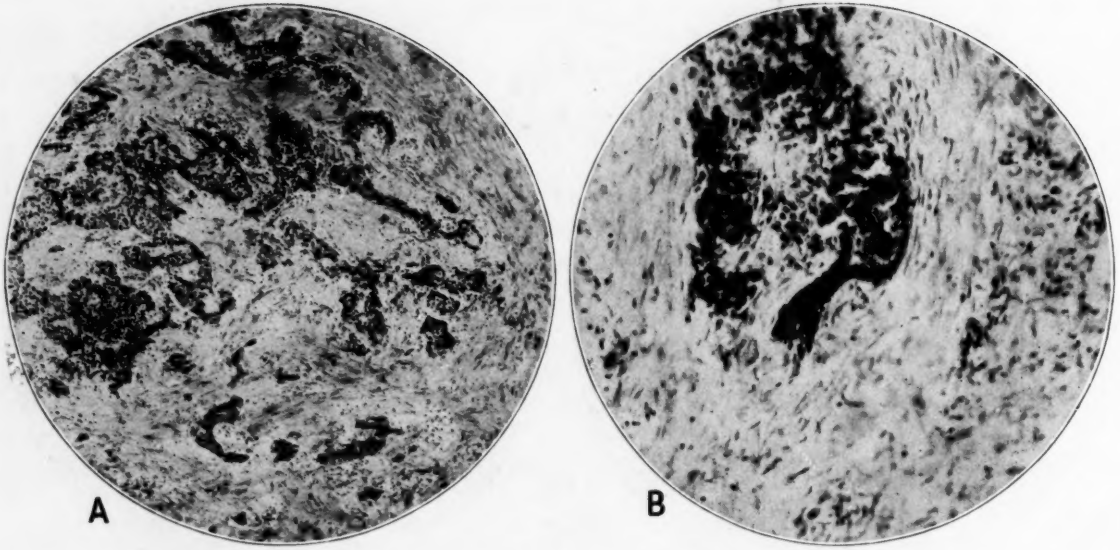


Fig. 3.—*A*, the capsule infiltrated by tumor cells (× 65); *B*, a pancreatic duct with tumor cells (× 180).

and degree of fibrosis. He demonstrated that in the early stages there was an intimate cell-capillary relationship resembling that of the normal pancreatic islet and that, as growth progressed, the parenchymal proliferation exceeded the vascular growth. Also, as the stage of tumor development advanced, there was a corresponding tendency to separation of the epithelial structures from the capillaries by deposition of increasing amounts of perivascular connective tissue. Degeneration and necrosis were observed in the presumably older portions of the tumors. O'Leary and Womack,[9] studying the material with which Bensley worked and two additional tumors, confirmed these observations.

In the portions of the tumor studied in our case we did not find anything comparable to the earliest stages of tumor growth described by Bensley. In no

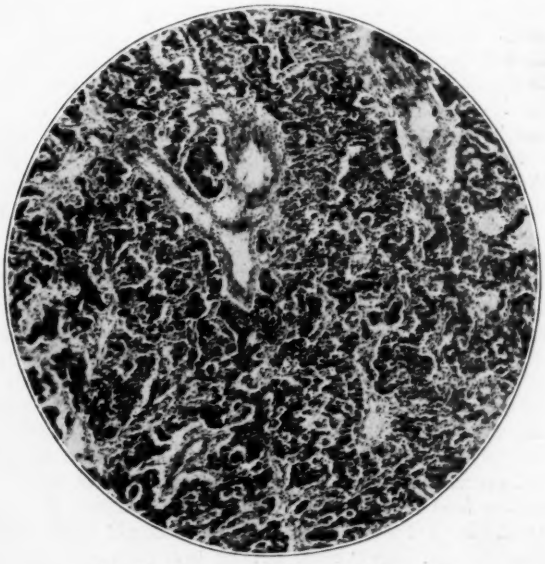


Fig. 4.—The general pattern of the tumor.

area did the cell-vascular accommodation appear as intimate as in the normal islet. The earliest stage of development noted in this tumor was in one area adjacent to the capsule, where the tissue resembled in its general appearance a huge island of Langerhans (fig. 4). This consisted of interlacing cords of epithelial cells, from 2 to 4 cells in thickness, separated by a fairly rich capillary network. Even these vessels, however, were invested with a thin layer of connective tissue.

Elsewhere the tumor was in a more advanced stage of development and for the most part consisted of thick cell cords and masses, separated by dense bands of connective tissue. In this region the vascular supply was less profuse, and large cell masses were interposed between widely separated capillaries. In those areas the deposition of connective tissue along the capillaries and around the

9. O'Leary, J. L., and Womack, N.: Histology of Adenoma of the Islets of Langerhans, Arch. Path. **17**:291 (March) 1934.

arterioles and small arteries was striking. This feature was even more marked around the larger blood vessels just within the capsule. A few cells throughout the tumor appeared degenerated; adjacent to the larger vessels with thickened peripheral connective tissue were small areas of cellular degeneration with hemorrhage. No hyalinization was observed.

Fixed in Zenker's solution (prepared according to the original formula, with acetic acid) and stained with hematoxylin and eosin and with Mallory's aniline-acid fuchsin stain, the component cells of this tumor resembled the cells of the islands of Langerhans. They were, however, somewhat larger than the cells comprising the individual islets observed elsewhere in the pancreas. They were polygonal where they were in contact; round or ovoid where discrete. The cell boundaries were distinct. With hematoxylin and eosin stain the cytoplasm was distinctly eosinophilic and in most instances agranular. Occasional cells showed fine granularity. The nuclei stained deeply, were fairly large, round to ovoid and of uniform size and shape and contained irregular chromatin accumulations. Some of the cells contained 2 mature nuclei. Rare bar-shaped mitoses were present.

With fixation in Zenker's solution and Mallory's aniline-acid fuchsin stain the cytoplasm had an appearance suggesting granularity, but no specific granules were seen. In some cells the granular cytoplasm was dull red; in others it was distinctly blue. Most of the cells contained large, spherical amorphous cytoplasmic masses which stained a deep brick red. They were as large as or larger than the nucleus; in some instances they were seemingly attached to the nuclear membrane, and in others, lying free in the cytoplasm.

Tissue fixed in Zenker's solution was sent to Professor Bensley, who applied his neutral gentian stain and the Bowie and the Mallory azan stains. He was unable to identify any specific granules but commented on the granular appearance of the cytoplasm. This, he said, may have been a coagulation phenomenon. With the azan method, he said, "practically every epithelial cell contains a mass of hyaline material as large as the nucleus. This stains distinctly blue. The nature of it, of course, is unknown."

Unfortunately for the studying of the granularity of the cytoplasm our material was fixed in the standard Zenker's solution, containing acetic acid, rather than in the more appropriate form of Zenker's solution in which solution of formaldehyde U. S. P. is used instead of the acetic acid. On the technic of fixation of tissues for a study of the granules, Lane[10] remarked: "It is of the utmost importance that acetic acid be carefully avoided, as I have found that even a few drops of this acid, after repeated trials with numerous fluids containing acetic acid, were enough to vitiate the entire work." Bowie,[11] however, obtained good results with fixation in solution containing acetic acid.

We are therefore at a loss to explain the significance of the absence of specific granules in this tumor. They may have been dissolved out by the acetic acid, or they may have been absent initially. Regarding this question Professor Bensley stated in a personal communication that the absence of specific granules "does not mean that the tumor did not cause the hypoglycemia, since these tumors

10. Lane, M. A.: Cytology of the Areas of Langerhans, Am. J. Anat. **7**:409, 1907.

11. Bowie, D. J.: Cytologic Studies of the Islets of Langerhans in a Teleost, Neomancis Griseus, Anat. Rec. **29**:57, 1924.

do not all behave alike in relation to stains and in particular the granules often fail to stain like either A or B granules with neutral gentian and Bowie's stains. In a neoplasm one must expect all grades of deviation from the normal."

We do not feel that this tumor was malignant. Partially encapsulated tumors of this type have been described [9] in which there was no evidence of malignancy. In this tumor there was no infiltration into the adjacent pancreatic tissue, nor was there extension into the blood vessels. Symptoms of hypoglycemia were present for almost six years, and laboratory confirmation was obtained more than four years before death occurred, and yet there were no metastases.

The thyroid gland was normal. Serial sections of the entire pituitary gland were examined and reported on by Dr. E. M. Butt as without significant deviation from the normal. The microscopic architecture of the thymus was normal. The Hassall corpuscles were almost uniformly hyalinized, although a few with cellular structure remained. The blood vessels were moderately congested. Hematoxylin and eosin and a stain for myelin sheaths in sections from the motor cortex of the brain, the angular gyrus and optic radiations revealed no pathologic condition. The myocardium was normal. In the lungs there were small areas of acute emphysema, with rupture of the alveolar walls. Adjacent to these were small patches of atelectasis. Many alveoli were filled with fluid transudate, while others contained small extravasations of blood. The vessels were moderately engorged. The polygonal cells in all portions of the hepatic lobule contained large amounts of fat, in many cases apparently completely replacing the cytoplasm. There was a moderate degree of periportal round cell infiltration. The splenic pulp was acutely congested with blood. The malpighian corpuscles were hyperplastic. The kidney was normal except for slight cloudy swelling of the tubular epithelium. There was marked engorgement of the entire vascular tree. The adrenal glands were normal. In the testis there was active spermatogenesis, but there appeared to be fewer interstitial cells than normal.

Sections of the liver stained for glycogen by the Best carmine method revealed large amounts of glycogen in the polygonal cells, an observation in agreement with presumable hyperinsulinism. Sections of the myocardium and kidney so stained revealed no glycogen granules.

Of incidental interest in this case, although in all probability of no immediate significance, was the presence of a so-called thymicolymphatic constitution, as evidenced by the persistence of the thymus, the hyperplasia of the lymphoid tissues of the spleen and intestine, the enlargement of the intra-abdominal lymph nodes and the hypoplasia of the aorta and the slight enlargement of the adrenal glands.

It is probable that the immediate cause of death in this case was asphyxia, the culmination of a hypoglycemic attack. Evidences of oxygen deprivation were the extreme cyanosis of the head and neck, the brain surfaces and the kidneys; the well marked vascular engorgement of the thoracic and abdominal viscera; the petechial hemorrhages in the pericardium and pleurae, and the presence of acute emphysema and atelectasis in the lungs.

Summary of the Pathologic Observations.—A tumor of the pancreatic islet cells was present which resembled in structure other tumors described in the literature. Specific granules were not seen, and a possible explanation for this is offered. Excessive glycogen stores in the liver corresponded with a presumable increase in the secretion of insulin.

CHARACTER OF THE HYPOGLYCEMIC ATTACKS

The hypoglycemic attacks in this case were numerous and varied. Frequently initial symptoms were hunger, weakness, anxiety, twitching of the right hand or right side of the face and numbness of the right hand. The patient utilized these symptoms as warnings and drank orange juice, which almost always gave rapid relief. Occasionally a convulsion occurred without any premonitory symptoms. In mild attacks, besides the aforementioned initial indications, there occurred nausea, vomiting, headache, drowsiness, trembling, perspiration, facetiousness, pugnacity, ataxia and loss of speech. Objectively, there were pallor, coldness of the extremities, tremor, profuse perspiration, dilatation of the pupils, a subnormal temperature and an increase in the pulse pressure. Tachycardia was present so much of the time (although no cardiac lesion was demonstrable) that it could not be utilized as an indication of hypoglycemia. More severe symptoms were aphasia; hemiparesis; confusion; involuntary laughing, crying and singing; delusions; hallucinations; convulsions, and coma. All of these were observed at different times. The type of symptom was not entirely dependent on the level of the blood sugar. Occasionally a low value for blood sugar (e. g., 32 mg. per hundred cubic centimeters) was recorded without any subjective or objective abnormality. However, in the presence of symptoms hypoglycemia was always found. A few of these symptoms call for more detailed analysis.

It is interesting that frequently there were minor personality changes incident to the lowered glycemic state. The patient, who ordinarily was quiet, pleasant and cooperative, would become stubborn or facetious and at times mean and surly, while apparently retaining all his normal capacities. It was repeatedly necessary to demonstrate his response to carbohydrate in these instances in order to convince the nurses in attendance that he was not wilfully uncooperative. For a short period this patient was cared for at the Los Angeles County Farm, where his ailment was considered largely hysterical. Here orange juice was withheld. He was returned to the hospital in a state of acute psychosis and for one week showed definite hallucinations and delusions.

The convulsive episodes were of particular interest. These also varied from time to time. Usually they were preceded by a long or short period during which the aforementioned hypoglycemic manifestations were present. As a matter of fact, the convulsions were usually the summation of increasing hypoglycemic effects and would in all probability have been more frequent if the falling level of the blood sugar had not been curbed early in its downward course. The preliminary period might be a few hours, and again the convulsions might occur without any premonitory symptom. The attacks varied also in their totality. Numbness of the right hand, twitching of the right hand

or right eyelid, right-sided jacksonian seizures and generalized convulsions, with or without residual hemiparesis and the Babinski reflex phenomena, each occurred as isolated manifestations. Almost always the patient regained consciousness rapidly after a convulsion, at which time the level of the blood sugar would have returned to normal.

The hypoglycemic symptoms occurred most frequently in the morning, when there had been the longest interval after eating. The nurses' notes frequently indicated "profuse diaphoresis" during the night, and the patient was often confused on being aroused for breakfast.

The clinical picture presented during hypoglycemia was no different from that observed in many other instances of hyperinsulinism. May we stress again the variability of symptoms from time to time and the occurrence of spells remote from the preceding meal and emphasize such special symptoms as the profuse perspiration, the subnormal temperature and the convulsive phenomena present in all types of qualitative and quantitative variants?

SPECIAL STUDIES

1. *Inorganic Phosphates of the Blood Serum.*—Injection of insulin in a normal subject causes a diminution in the content of organic phosphates in the blood as well as in the sugar content.[12] These changes coincide with the modern interpretations of muscle metabolism. Hexose phosphate is considered to be an intermediary product in muscle metabolism. Insulin, in storing muscle glycogen, is thought to convert blood sugar and blood phosphates into hexose phosphate; hence the diminution in the phosphate and sugar contents of the blood after the injection of insulin. Similarly, a high carbohydrate feeding also depresses the phosphate content, presumably by inducing the secretion of insulin. During muscular activity this process is reversed; glycogen breaks down to hexose phosphate and then to lactic acid, with the release of phosphates into the blood stream. Corresponding with this concept, Harrop found the phosphate level elevated subsequent to strychnine convulsions in rabbits.

The content of sugar and phosphate in the blood was determined in five instances at variable periods after breakfast. The patient had breakfast at 7 a. m., and usually dextrose was given in some form at 8 o'clock to assure a high level for blood sugar when tests were carried out. Blood sugar determinations were made by the Benedict method[13] and blood phosphate determinations by the method of Benedict and Theis.[14] In two tests the values for the calcium, the total protein, the volume and the carbon dioxide-combining power also were obtained. The results are shown in table 1.

12. Harrop, G. A., Jr., and Benedict, E. M.: The Participation of Inorganic Substances in Carbohydrate Metabolism, J. Biol. Chem. **59**:683, 1924.

13. Benedict, S. R.: The Estimation of Sugar in Blood and Normal Urine, J. Biol. Chem. **68**:759 (June) 1926.

14. Benedict, S. R., and Theis, R. C.: A Modification of the Molybdic Method for the Determination of Inorganic Phosphorus in Serum, J. Biol. Chem. **61**:63, 1924.

TABLE 1.—*Serial Readings of the Blood Sugar and Serum Inorganic Phosphate Values*

Date	Tests	Data							Comment
9/12/33		9:30 a.m.	10:30 a.m.	11:00 a.m.	11:45 a.m.				7 a.m., breakfast
	Blood sugar, mg. per 100 cc.	91.0	58.0	51.0	41.0	....	....	....	8 a.m., 500 cc. of orange juice
	Blood phosphates, mg. per 100 cc.	3.8	5.5	5.5	7.6	....	....	....	9:30 a.m., 250 cc. of orange juice
9/15/33		11:15 a.m.	11:40 a.m.	12:45 p.m.	1:35 p.m.	2:20 p.m.			Convulsion in the morning
	Blood sugar, mg. per 100 cc.	178.0	104.0	40.0	33.0	37.0	....	....	10 a.m., 1,000 cc. of orange juice; 1 cc. of
	Blood phosphates, mg. per 100 cc.	3.8	3.8	4.5	4.5	4.5	....	....	epinephrine, hypodermically
9/19/33		9:00 a.m.	9:40 a.m.	10:10 a.m.	10:40 a.m.	11:10 a.m.	11:35 a.m.	1:30 p.m.	7:14 a.m., breakfast
	Blood sugar, mg. per 100 cc.	73.0	64.0	63.0	52.0	52.0	41.0	45.0	11:40 a.m., 750 cc. of orange juice; 10 cc. of
	Blood phosphates, mg. per 100 cc.	3.5	3.7	....	3.7	3.7	4.4	4.2	50 per cent solution of dextrose intravenously
	Blood calcium, mg. per 100 cc.	12.7	12.2	....	12.8	13.0	12.8	13.0	12 m., two sandwiches and milk
9/22/33		8:50 a.m.	11:15 a.m.	1:20 p.m.					7 a.m., breakfast
	Blood sugar, mg. per 100 cc.	164.0	47.0	116.0	....	....	....	....	8 a.m., 500 cc. of orange juice
	Blood phosphates, mg. per 100 cc.	4.0	5.3	5.1	....	....	....	....	
	Blood calcium, mg. per 100 cc.	13.0	13.0	13.0	....	....	....	....	
9/29/33		9:15 a.m.	10:20 a.m.	11:15 a.m.	11:30 a.m.	1:45 p.m.			7 a.m., breakfast
	Blood sugar, mg. per 100 cc.	50.0	42.0	C*	68.0	53.0	....	....	8 a.m., 500 cc. of orange juice
	Blood phosphates, mg. per 100 cc.	3.5	3.5	....	5.6	4.1	....	....	

* Convulsion.

Whenever the sugar level was low, the level for inorganic phosphates rose. In one instance after a convulsion there was a marked increase in the phosphate level. The values for the calcium, the total protein, the volume and the carbon dioxide-combining power did not vary with the different levels for blood sugar. The rise in the phosphate content in this patient with hyperinsulinism was in contrast to the results of the injection of insulin. With insulin or with insulin plus dextrose,[15] a fall in the phosphate level manifests itself within the first hour and may persist for only from one to three hours. Since initial determinations of the sugar content in our studies were obtained more than one hour after the taking of dextrose, an initial drop in the phosphate content may have been missed. These studies will therefore need to be repeated before our findings can be properly evaluated. The conditions of our tests differed from the insulin experiments in at least two other particulars which may be significant. First, there was present in our patient presumably an excessive amount of insulin, continuously or at least for prolonged periods, in place of transient hyperinsulinism following the injection of insulin. Second because of the absolute necessity for frequent feedings, our tests were not performed in the postabsorptive state. As stated, our data are difficult to evaluate. The finding of interest is that the phosphate content of the blood was high and increasing when the sugar content was low and falling. Further studies in regard to this matter on patients with hyperinsulinism may prove of value.

2. *Psychomotor Reactions.*—As hypoglycemia produces such marked changes in mental functions, it was desirable to note at what stage the earliest psychic manifestations appeared.

The procedure adopted consisted in withholding food and obtaining blood sugar determinations, noting hypoglycemic symptoms and recording reactions to special tests at repeated intervals. Three trials were employed at each test. In the association tests five words were submitted, and opposite responses were requested. Scoring was done on the basis of correct responses without consideration of the time element. Strength was indicated by the hand grip, as measured with the dynamometer. The average was taken from two trials each with the right and left hands. Speed was measured by the number of revolutions on a finger counter during the first thirty seconds. The number of revolutions during the next thirty seconds was taken as a measure of endurance. The progressive fall in the sugar content of the blood limits the time and hence the number of tests which can be made at any one level. The results are indicated in table 2.

The earliest hypoglycemic effect on the psychomotor reactions was a decrease in the auditory memory span for sentences, except once, when defective association processes were noted sooner. Impairment of mathematical ability and disorientation occurred at later lower hypo-

15. Ellsworth, R.: Secondary Alterations in Total Serum Calcium After the Administration of Glucose and Insulin, J. Clin. Investigation **8**:139 (Feb.) 1930.

TABLE 2.—*Results of Psychomotor Tests at Various Hypoglycemic Levels*

			Memory Span*				Motor Tests			Hypoglycemic Signs and Symptoms				Blood Pressure, Mm. of Mercury		
Date	Time	Blood Sugar, Mg. per 100 Cc.	Digits	Words	Sentences	Association Test	Strength	Speed, Revolutions	Endurance, Revolutions	Pupils	Tremor	Perspiration	Pulse Rate	Systolic	Diastolic	Other Symptoms
8/22/33	10:30 a.m.	51	3	3^2	2^1	..	...	...	...	0	0	0	108	...	...	
	11:00 a.m.	48	3	2	1^1	..	...	...	...	Moderate dilatation	+	0	108	...	...	Vacant stare
	11:30 a.m.	36	3?	0	0	..	...	...	...	Moderate dilatation	++	—	120	...	...	Twitchings in right arm, mannerisms (facial)
	12:00 m.	65	4^2	4^2	2	..	...	...	...	0	0	0	120	...	...	
8/29/33	9:45 a.m.	47	3	..	..	..	176	24	28	0	++	+	120	...	...	
	10:30 a.m.	43	3	..	..	..	160	37	33	0	+++	0	120	...	...	Clearing of throat; perseveration; mannerisms; stereotypy
	11:00 a.m.	42	1	..	..	..	140	0	0	Dilated	++++	0	144	...	...	Irresponsible; poor cooperation
	11:45 a.m.	142	5		..	..	182	101	105	0	+	+	132	...	...	
9/12/33	9:30 a.m.	91	5	..	3	5	153	65†	47	Moderate dilatation	0	?	120	130	100	
	10:20 a.m.	58	5	..	2	5	155	99	64	Dilated	0	?	112	156	104	
	11:00 a.m.	51	4	..	2	5	150	103	47	Dilated	+	0	84	144	90	
	11:45 a.m.	41	3	..	1	1	130	24‡	65	Dilated	++	0	118	158	108	Weak
9/15/33	11:15 a.m.	178	5	..	3^1	5	200	128	100	0	+	0	144	130	80	Weak
	11:45 a.m.	104	5	..	3	5	190	129	104	0	+	0	148	130	96	
	12:45 p.m.	40	4	..	1	P§	196	113	90	0	+++	+	130	146	100	Apathetic; clears throat
	1:35 p.m.	33	4	..	1	3	193	113	96	0	++	0	128	136	104	Apathetic
	2:30 p.m.	37	3	..	1	P§	155	87	68	0	+++	+	120	132	90	Drowsy; blinking; gross tremor; mannerisms; stereotyped speech
9/19/33	9:00 a.m.	73	4	..	3	5	195	127	112	4 mm.	?	?	120	146	106	
	9:40 a.m.	64	5	..	3	5	175	132	90	4 mm.	?	0	120	146	100	
	10:10 a.m.	63	4	..	2	2	183	117	96	5 mm.	?	0	114	158	110	Nervous
	10:40 a.m.	52	4	..	3^2	1	155	110	83	5 mm.	+	0	118	140	108	Apathetic; stereotyped actions
	11:10 a.m.	52	3	..	1	0	158	0	0	5 mm.	+++	0	132	152	120	Confused; catatonic
	11:35 a.m.	41	0	..	0	..	0	0	0	0	—	0	...	...	...	Restlessness, generalized twitchings
	1:30 p.m.	45	5	..	4	..	185	129	97	0	+?	0	120	126	80	Thrashing about

* The superior numbers indicate the number of tests.
† The patient had not learned the technic.
‡ Poor cooperation.
§ P indicates perseveration.

glycemic levels. Abnormalities in the psychic functions suggested a depression of the sugar level before tremor, perspiration, dilatation of the pupils or other general hypoglycemic symptoms were evident. Since the patient had a rapid pulse at all times, tachycardia could not be correlated with hypoglycemia in this case. The psychologic functions manifested impairment at higher glycemic levels than did the motor. Speed and endurance diminished with increasing hypoglycemia; these were more sensitive than tests for strength.

This study reveals the early vulnerability of auditory verbal memory. Our tests indicate that the earliest interference is with psychic rather than with muscular functions. Similar results were obtained in a study by Dashiell [16] on a diabetic patient receiving insulin, although no readings for the blood sugar were taken and the work on the whole was qualitative rather than quantitative. The early involvement of memory processes during hypoglycemia calls to mind the frequency of impairment of memory in the organic syndromes in psychiatric disorders.

3. *Sugar Content and Pressure of Spinal Fluid.*—The spinal fluid changes with variations in the concentration of sugar in the blood stream. With the induction of hyperglycemia, the spinal fluid pressure becomes depressed; with hypoglycemia, it becomes elevated.[17] The spinal fluid, according to a well substantiated theory, is a "dialysate in osmotic and hydrostatic equilibrium with the blood plasma." [18] This would call for modifications in the spinal fluid pressure on the basis of the concentration of sugar not only in the blood but also in the spinal fluid. Normally the content of sugar in the spinal fluid is from 50 to 70 per cent of that in the blood and varies in the same direction as the sugar content of the blood. A change in the sugar content of the blood is followed by a latent period of from two to five hours before the equilibrium between the sugar in the blood and that in the spinal fluid is reestablished, apparently the period of time required for permeability adjustments through the hemato-encephalic barrier.[19] The great fluctua-

16. Dashiell, J. F.: Variations in Psycho-Motor Efficiency in a Diabetic with Changes in the Blood Sugar Level, J. Comp. Psychol. **10**:189, 1930.

17. Weed, L. H., and McKibben, P. S.: Pressure Changes in the Cerebrospinal Fluid Following Intravenous Injection of Solutions of Various Concentrations, Am. J. Physiol. **48**:512, 1919.

18. Fremont-Smith, F.; Thomas, G. W.; Dailey, M. E., and Carroll, M. P.: The Equilibrium Between Cerebrospinal Fluid and Blood Plasma, Brain **54**:303, 1931.

19. Gregersen, M. I., and Wright, L.: Effect of Intravenous Injection of Sucrose and Glucose upon Reducing Power of Cerebrospinal Fluid, Before and After Hydrolysis, Am. J. Physiol. **112**:97 (May) 1935. Goodwin, G. M., and Shelley, H. J.: The Sugar Content of the Cerebrospinal Fluid and Its Relation to the Blood Sugar, Arch. Int. Med. **35**:242 (Feb.) 1925.

tions of the level of the blood sugar in cases of hyperinsulinism offer an opportunity for checking many of these physiologic principles.

Therefore, determinations of the spinal fluid pressure and the sugar content of the blood and spinal fluid were obtained at varying levels of the blood sugar after food had been withheld. The spinal fluid pressure was always taken with the patient in a horizontal position. The results are presented in table 3. Before these results can be evaluated, it is necessary to take into consideration some of the experimental difficulties

TABLE 3.—*Values for the Sugar Content of the Blood and Spinal Fluid and the Spinal Fluid Pressures at Various Hypoglycemic Levels*

Date	Time	Blood Sugar, Mg. per 100 Cc.	Spinal Fluid Sugar, Mg. per 100 Cc.	Spinal Fluid Pressure, Mm. of Mercury	Symptoms
11/ 5/31		88	75	250	
3/29/32		41	40	...	
3/16/33	9:00 a.m.	111	..	...	None
	10:15 a.m.	81	83	147*	None
	11:30 a.m.	47	66	205	None
	12:30 p.m.	46	..	...	None
	1:30 p.m.	46	37	262	Drowsy; restless; singing incoherently
3/30/33	8:30 a.m.	111	..	...	
	9:00 a.m.	146	..	...	
	11:00 a.m.	85	98	175†	
	11:30 a.m.	53	83	150	
	12:00 m.	49	77	150	
	12:30 p.m.	39	63	150	
	1:00 p.m.	38	50	...	1:15 p.m., tremor; blinking of eyes
	1:30 p.m.	48	48	...	1:30 p.m., smacking of lips; clearing of throat; numbness of feet; restlessness
	2:00 p.m.	38	42	...	2:00 p.m., singing; whining; facetiousness; perspiring; disoriented (did not know date); could not multiply 7×9 or add 2+3

* Spinal puncture at 10:15 a.m.; needle left in place until 11:30 a.m.; 5 cc. of fluid removed at 10 and 11:30 a.m. Second puncture performed at 1:30 p.m.; this fluid was slightly blood tinged throughout; the bloody contamination probably occurred at the time of withdrawal of the needle at 11:30, since the puncture wound then bled freely and the subcutaneous tissue became distended.

† Spinal puncture at 11 a.m.; needle left in situ until 1 p.m. Needle reinserted at 1:30 p.m. and removed at 2 p.m.; 5 cc. of fluid withdrawn for the first four sugar determinations; 3 cc. for subsequent tests.

involved. These apply only to serial observations. First, the withdrawal of spinal fluid for sugar determinations markedly lowers the spinal fluid pressure. Hence, combined serial readings for the sugar content and the pressure of the spinal fluid are not possible, and the values for the spinal fluid pressures obtained after the initial reading must be discounted in our studies. When, however, the spinal fluid pressure rises at subsequent readings (as in the study of Nov. 16, 1933) the increase in pressure must be accepted as indicating the general direction, though it cannot be the absolute value. Apparently the rise was sufficiently great to overshadow the loss due to the withdrawal of spinal fluid, or the interval was long enough to permit replacement of the

lost fluid. Second, leakage at the site of puncture is a factor which may affect subsequent pressure readings. This necessitates leaving the needle in place throughout the entire study. Third, the needle as a foreign body probably excites a local inflammatory reaction when in place for any prolonged period, and this may elevate the pressure. Finally, there is a possibility that the spinal puncture itself may alter the permeability of the hemato-encephalic barrier. Both of the latter possibilities require normal controls and cannot be properly evaluated in this study. Despite these considerations, the initial readings are all valid. The subsequent determinations of the sugar content of the blood and spinal fluid also represent the true state of affairs, unless alterations in the permeability of the hemato-encephalic barrier were induced. Although subsequent readings of the spinal fluid pressure have definite limitations as to their absolute accuracy, the general trend or direction can be accepted for the readings on March 16, 1933, for the reasons already given.

The following conclusions from this study appear warranted: Low values for blood sugar or hypoglycemic states are associated with an increase or elevation of the spinal fluid pressures. A definite latent period exists between the time of a change in the value for blood sugar and restoration of the equilibrium of the blood sugar-spinal fluid sugar ratio. This is apparent from the results in table 3, and since the fall in the value for blood sugar was rapid in this patient and the latent period was relatively long, it leads to the paradoxic situation in which the sugar content of the spinal fluid is even higher than that of the blood during part of the period of readjustment. It is of interest that during the study of March 16, 1933, the sugar content of the blood remained stationary at 47 mg. per hundred cubic centimeters for two hours. During that time the sugar content of the spinal fluid dropped from 66 to 37 mg. per hundred cubic centimeters, and hypoglycemic symptoms appeared only toward the end of this interval. Since low values for the sugar content of venous blood may exist without symptoms, the foregoing observation suggested a possible correlation between low sugar levels for the spinal fluid and the development of "hypoglycemic" symptoms. This thought was rudely disturbed by the observation in another patient with hyperinsulinism [20] that hypoglycemic symptoms were present when the sugar level of the blood was low but that of the spinal fluid was high, higher than the level for the blood.

4. *Intradermal Saline Test.*—The intradermal saline test of McClure and Aldrich [21] was performed at different levels of hypoglycemia.

20. Ziskind, E., and Bailey, W.: Hyperinsulinism: Report of a Second Case with Anatomic Findings, to be published.

21. McClure, W. B., and Aldrich, C. A.: Time Required for Disappearance of Intradermally Injected Salt Solution, J. A. M. A. **81**:293 (July 28) 1923.

Absorption of the wheals always required more than an hour, which is longer than the normal rate.

The test indicates that no state of dehydration exists in the skin, although Drabkin and Shilkret [22] have demonstrated anhydremia after an injection of insulin. If anything, the tissues of our patient may have been in a state of increased hydration. This observation is based on only an isolated uncontrolled experiment and is presented as such.

5. *Effect of Mental Work on Sugar Content of Blood.*—Modern researches indicate that there is no storage of dextrose in the brain and that the nervous system is directly dependent on the sugar and lactic acid in the blood for its fuel supply. In hypoglycemic states the adequacy of this supply is interfered with. If mental work utilizes energy from the combustion of carbohydrates, such an increased demand for fuel might result in an early precipitation of hypoglycemic symptoms in a patient with hyperinsulinism.

TABLE 4.—*Results of Intradermal Saline Test*

Time when wheals were made	9:15 a.m.	9:55 a.m.	10:30 a.m.*
Blood sugar, mg. per 100 cc.	50		42
Disappearance of wheals	1 hour plus	1 hour plus	1 hour plus

* Convulsions occurred at 11:15 a.m.

To test this, our patient performed additions for thirty minutes at six different sessions. Blood sugar determinations were made before and after each test period and also for thirty minute control periods preceding and following the test. The development of hypoglycemic symptoms also was recorded.

The results were inconclusive. The mental work did not produce a sufficient increase in the consumption of dextrose by the brain to be reflected in a recognizable depression of the sugar level of the blood.

SUMMARY AND CONCLUSIONS

A report is made of the clinical course of a patient with hyperinsulinism who was observed for four years (most of the time in a hospital). Necropsy revealed an adenoma of the pancreatic islets which had not been discovered at two previous pancreatic resections.

Dinitrophenol had a retarding effect on the increasing obesity. This result and the physiologic indications for the drug in these cases would indicate its further trial for symptomatic relief, particularly in hypoglycemia not amenable to surgical intervention, were it not for the severe toxic effects sometimes noted when this drug is used.

The variability in the hypoglycemic attacks is stressed.

22. Drabkin, D. L., and Shilkret, R.: Insulin Anhydremia, Am. J. Physiol. **83**:141, 1927.

A rise in the content of inorganic phosphates in the blood was discovered during the hypoglycemia present in our patient after the ingestion of dextrose. Further studies are indicated, since a fall in the phosphate content is reported in insulin hypoglycemia.

Impairment of psychologic functions, e. g., an effect on the memory span, was among the earliest signs of insulin hypoglycemia.

The spinal fluid pressure is elevated in a hypoglycemic state. In our patient the latent period between the drop in the sugar content of the blood and the ultimate fall in the sugar content of the spinal fluid was so long that the level in the spinal fluid during part of this interval was at a higher level than that in the blood.

The intradermal saline test did not reveal a state of dehydration in the skin during the hypoglycemic phase.

The effect of mental work on the level of the blood sugar was tested, but the results were inconclusive.

2007 Wilshire Boulevard.

ROLE OF THE ARTERIES IN THE PERIPHERAL RESISTANCE OF HYPERTENSION AND RELATED STATES

ENID TRIBE OPPENHEIMER, B.Sc.
AND
MYRON PRINZMETAL, M.D.*
NEW YORK

It seems established that arterial hypertension must be due to increased peripheral resistance, since the other factors which are involved in the maintenance of blood pressure—cardiac output,[1] volume of the blood [2] and viscosity of the blood [3]—have been proved to be normal in patients with hypertension. Since it has recently been shown that the blood flow in the arm is normal in hypertensive patients,[4] it is probable that the increase in resistance is widespread, affecting all parts of the body and not merely, as had been suggested, the splanchnic or other localized areas. Moreover the increased resistance must be due to hypertonicity of the vessels, i. e., a functional constriction, not due to a structural narrowing, since relaxation of these hypertensive vessels can be obtained.[4a] The evidence concerning the exact cause of the increased peripheral resistance is still somewhat negative, since it has

* Sutro Fellow for Cardiovascular Research.
From the Medical Service of the Mount Sinai Hospital.

1. (*a*) Lauter, S., and Baumann, H.: Ueber den Kreislauf bei Hochdruck, Arteriosklerose und Apoplexie, Ztschr. f. klin. Med. **109**:415 (Dec.) 1928. (*b*) Burwell, C. S., and Smith, W. C.: The Output of the Heart in Patients with Abnormal Blood Pressures, J. Clin. Investigation **7**:1 (April) 1929. (*c*) Weiss, S., and Ellis, L. B.: The Quantitative Aspects and Dynamics of the Circulatory Mechanism in Arterial Hypertension, Am. Heart J. **5**:448 (April) 1930. (*d*) Gladstone, S. A.: Cardiac Output and Arterial Hypertension, New York, The Author, 1935.

2. Linder, G. C.; Lundsgaard, C.; Van Slyke, D. D., and Stillman, S.: Changes in the Volume of Plasma and the Absolute Amount of Plasma Proteins in Nephritis, J. Exper. Med. **39**:921 (June) 1924.

3. (*a*) Austrian, C. R.: The Viscosity of the Blood in Health and Disease, Bull. Johns Hopkins Hosp. **22**:9 (Jan.) 1911. (*b*) Friedman, B., and Prinzmetal, M.: Vasomotor Effects of Blood in Patients with Hypertension, Proc. Soc. Exper. Biol. & Med. **34**:543 (May) 1936.

4. (*a*) Prinzmetal, M., and Wilson, C.: The Nature of the Peripheral Resistance in Arterial Hypertension with Special Reference to the Vasomotor System, J. Clin. Investigation **15**:63 (Jan.) 1936. (*b*) Pickering, G. W.: Peripheral Resistance in Persistent Arterial Hypertension, Clin. Sc. **2**:209 (May) 1936.

been shown not to be of neurogenic origin [4] and not to be due to any pressor substance having a direct effect on the vessels.[5] Evidence has recently been obtained which indicates that a pressor substance normally present in the kidneys is probably increased in dogs with experimentally produced hypertension [6] and in patients with essential and "renal" hypertension.[6b]

The present paper deals with the question of which part of the vascular bed is concerned with the increase in peripheral resistance. It is conceivable that narrowing might occur in any of the four main subdivisions of the peripheral circulation—arteries, arterioles, capillaries or veins. It has, however, been known for some time that there is no rise in venous pressure in hypertensive conditions, and it has more recently been shown that capillary pressure also is normal.[7] For these and other reasons it seems probable that neither the veins nor the capillaries are responsible for the rise in blood pressure.

On theoretical grounds, since the arterioles normally contribute by far the major part of the peripheral resistance, it seems probable that constriction of these vessels may be responsible for the tremendous rise in resistance in hypertension. The finding by Weiss and Ellis [8] that arteriolar pressure is increased in hypertensive conditions supports this contention. Whether or not the larger arteries also are abnormally constricted remains uncertain.

There appears to be no doubt that spasm of the retinal vessels may occur in patients with eclampsia, malignant hypertension and nephritis; and Moschcowitz [9] has reported that in certain cases of acute nephritis there is an increased tonus of the radial artery. More recently, Weiss and his co-workers [10] have shown that even when there is a high pulse

5. Pickering, G. W.: The Effect of Introducing Blood from Patients with Essential Hypertension into Other Human Subjects, Clin. Sc. **2**:185 (May) 1936. Friedman and Prinzmetal.[3b]

6. (*a*) Harrison, T. R.; Blalock, A., and Mason, M. F.: Effects on Blood Pressure of Injection of Kidney Extracts of Dogs with Renal Hypertension, Proc. Soc. Exper. Biol. & Med. **35**:38 (Oct.) 1936. (*b*) Prinzmetal, M., and Friedman, B.: Pressor Effects of Kidney Extracts from Patients and Dogs with Hypertension, ibid. **35**:122 (Oct.) 1936.

7. Ellis, L. B., and Weiss, Soma: The Measurement of Capillary Pressure Under Natural Conditions and After Arteriolar Dilatation in Normal Subjects and in Patients with Arterial Hypertension and with Arteriosclerosis, J. Clin. Investigation **8**:47 (Dec.) 1929.

8. Weiss and Ellis.[1c] Ellis and Weiss.[7]

9. Moschcowitz, E.: Pseudo, or Transient, Arteriosclerosis, J. A. M. A. **90**: 1526 (May 12) 1928.

10. Weiss, Soma; Haynes, F. W., and Shore, R.: The Relation of Arterial Pulse Pressure to the Hemodynamics of Arterial Hypertension, Am. Heart J. **11**:402 (April) 1936.

pressure the cardiac output of hypertensive patients remains essentially normal. According to Wiggers,[11] who worked with an artificial circulation, an increased pulse pressure with a normal cardiac output indicates a diminution of arterial elasticity. Weiss therefore concluded that the hypertension must be due not only to increased resistance in the arterioles but also to physical changes in the arterial wall. The attempt by the same authors to show roentgenographically that the arteries themselves become narrowed in hypertensive conditions was inconclusive. This result might have been foretold, since by Poiseuille's law the pressure varies inversely with the fourth power of the radius, and consequently even the greatest possible rise in blood pressure would be due to a variation in diameter of such a minute dimension that it would be well within the limits of error of observation.

METHOD

Since, according to Poiseuille's law, the pressure in the vascular system is proportional to the resistance, the gradient, or fall, in pressure in passing from large to small arteries, through arterioles to capillaries and veins, is determined by the resistance in the different parts of the system. It seemed, therefore, that a study of pressure in large and in small arteries of normal and of hypertensive persons might reveal whether there is any change in the pressure gradient with a rise in blood pressure.

If the pressure gradient from large to small arteries should become steeper with the rise in systolic pressure in hypertension, it would point to an increased resistance in the larger arteries. If, on the other hand, the gradient should be lessened or should remain unchanged in hypertension, it would indicate that the increased resistance is on the arteriolar side, not in the arteries.

We therefore determined the blood pressure in the brachial artery by the usual auscultatory method and in the digital artery by a modification of the method of Gärtner.[12]

The subjects included twenty-five persons with normal, fifty-one with raised and fourteen with low blood pressure. Of the hypertensive patients, nine had malignant, 10 secondary, or "renal," and thirty-two "benign" hypertension. We were careful to exclude subjects having congestive heart failure, aortic insufficiency or severe anemia.

Observations were also made in cases of peripheral vascular abnormalities of various types, including thrombo-angiitis obliterans, thrombosis of the brachial

11. Wiggers, C. J.: Physical and Physiological Aspects of Arteriosclerosis and Hypertension, Ann. Int. Med. **6**:12 (July) 1932.

12. Gärtner, G.: Ueber einen neuen Blutdruckmesser (Tonometer), Wien. med. Wchnschr. **49**:1412 (July 22) 1899. Formijne, P.: Investigation of the Patency of Peripheral Arteries, Am. Heart J. **10**:1 (Oct.) 1934.

artery and sclerodactylia, and in one case of pheochromocytoma associated with paroxysmal hypertension.

Details of Method.—For determining the pressure in the digital artery we used a Gärtner capsule,[12] applying it to one of the digits, preferably the third (middle) digit. According to this method the finger is inserted into a hollow metal cuff or cylinder (fig. 1) made of appropriate size and shape to fit the finger loosely. This cuff is lined with a thin rubber membrane (part of a finger-cot), tied firmly over the two ends. The interior of this capsule is connected by means of a side tube with the mercury manometer of an ordinary blood pressure apparatus. To make the determination the finger is first rendered anemic by pushing on to it, from tip to base, a rather tight rubber ring; the capsule is placed over the middle phalanx of the finger, and the pressure is raised until it is higher than that expected in the digital artery. The rubber ring is then cut so that the blood flows into the finger up to the capsule, and the pressure in the capsule is slowly reduced until, at a certain pressure, the tip of the finger beyond the cuff is suddenly filled with blood. The pressure at which this flushing occurs is assumed to be the systolic pressure in the digital artery.

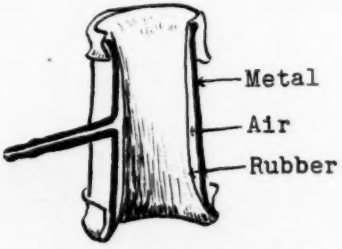


Fig. 1.—Section through the capsule of Gärtner (adapted from Formijne).

Both the brachial and the digital pressure were taken with the patient in the recumbent position, with the usual precautions of having the patient rest before the determination and keeping the artery under investigation at the level of the heart.

Determinations of brachial pressure were made at least twice—at the beginning and at the end of each series of observations—and usually more frequently, alternating with the determinations of digital pressure. The number of determinations of the digital pressure varied from five to ten, depending on the degree of variation between the different observations.

No significant differences in pressure could be observed in the different fingers or with natural variations in the temperature of the skin of the hand.

RESULTS

The results of our observations are summarized in tables 1 to 5 and are shown graphically in figures 2 and 3.

For the twenty-five control patients (table 1) with a normal blood pressure we found an average brachial systolic pressure of 124 mm. of mercury and a brachial diastolic pressure of 73 mm., giving a pulse pressure of 50 mm. The average digital systolic pressure was 95 mm.:

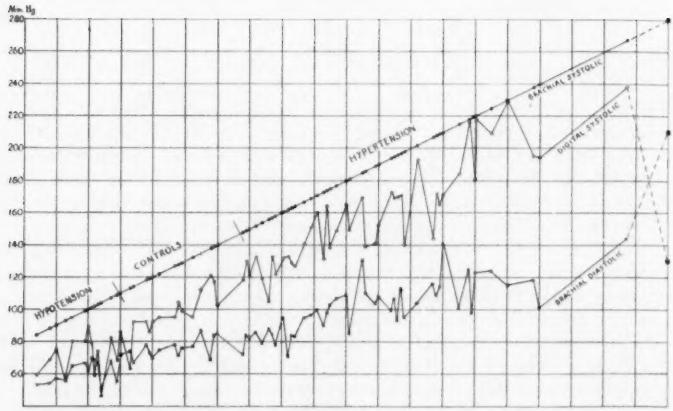


Fig. 2.—Chart showing the brachial systolic, digital systolic and brachial diastolic pressures of seventy-four persons, including hypotensive and hypertensive patients and controls. The last values at the right are for a patient with pheochromocytoma.

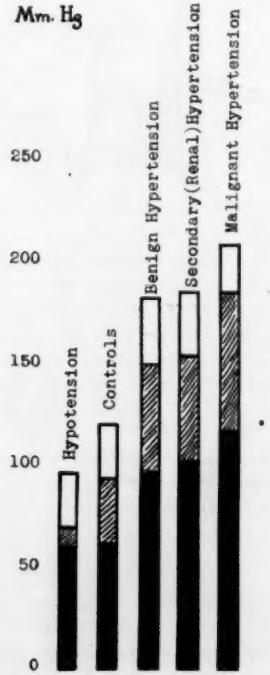


Fig. 3.—Chart of the blood pressure readings. The white column indicates the brachial systolic pressure; the shaded column, the digital systolic pressure, and the black column, the brachial diastolic pressure.

that is, the average difference between the brachial and the digital systolic pressure was 29 mm., thus agreeing with the results of earlier workers.[13]

For the fifty-one hypertensive patients (table 2) our figures showed an average brachial systolic pressure of 188 mm., a brachial diastolic pressure of 102 mm. (that is, a pulse pressure of 86 mm.) and an average digital systolic pressure of 159 mm. The average difference between the brachial and the digital systolic pressure was 29 mm. The pressure gradient therefore remained practically unchanged.

If among the hypertensive patients we consider only the group of patients with malignant hypertension (table 2C), we find some indication

TABLE 1.—*Data for Twenty-Five Controls*

Case No.	Age	Sex	Pressure, Mm. of Mercury: Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial-Digital Gradient	Clinical Diagnosis
1a	27	M	140	85	55	102	38	Normal
1b	27	M	133	77	56	95	38	Normal
1c	27	M	119	73	46	86	31	Normal
3	28	M	128	72	56	104	24	Hemophilia
4	17	M	110	73	36	92	18	Convalescent from rheumatic fever
5	54	M	120	71	41	93	27	Obstructive jaundice
6	40	M	110	76	34	70	40	Convalescent from ileitis
8	24	F	135	87	48	112	23	Nonmalignant bronchial bleeding
10	32	M	127	83	44	87	41	Convalescent from acute nephritis
13	45	F	110	68	38	96	14	Normal
14	14	M	120	70	50	86	34	Convalescent from lobar pneumonia
19	44	M	127	80	47	96	33	Convalescent from diabetes, hepatic cirrhosis and acute nephritis
20	26	M	113	74	39	63	50	Convalescent
23	30	M	127	71	56	102	25	Cough; hemoptysis
27a	25	M	129	74	55	99	30	Normal
27b	25	M	120	70	50	94	26	Normal
27c	25	M	118	70	48	84	34	Normal
28	55	M	114	67	47	95	19	Convalescent from bronchopneumonia
36	42	M	110	68	42	75	35	Convalescent from bronchiectiasis; afebrile
45b	35	M	118	86	32	101	17	Convalescent from acute nephritis
55	56	M	139	84	55	117	22	No arteriosclerosis
56	48	F	148	72	76	118	30	Surgical menopause
58b	16	F	114	20	94	89	25	Convalescent acute nephritis
62	52	F	138	69	69	121	17	Normal
86	35	F	122	75	47	95	27	Normal pressure on right side; left side, obliterative vascular disease
Averages.....			124	73	50	95	29	

that the digital pressure tends to approach the brachial pressure. The patients with malignant hypertension, with a brachial systolic average of 210 mm., had a diastolic pressure of 118 mm., a pulse pressure of 92 mm. and an average digital systolic pressure of 186 mm. The digital pressure was therefore only 24 mm. below the brachial pressure, and there was a slight decrease in the average pressure gradient.

As will be seen from figure 2, for three patients with hypertension with extremely high brachial pressure we actually found digital pressure

13. Cohn, A. E., and Lundsgaard, C.: A Study of the Blood Pressure by the Method of Gärtner, Especially in Patients Suffering from Fibrillation of the Auricles, J. Exper. Med. **27**:487 (April) 1918. Wishart, G. M.: Blood-Pressure Observations with a New Type of Oscillometer, Clin. Sc. **1**:159 (Dec.) 1933.

TABLE 2.—*Data for Fifty-One Hypertensive Patients*

Case No.	Age	Sex	Pressure, Mm. of Mercury: Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial-Digital Gradient	Clinical Diagnosis
A. Benign hypertension (32 patients)								
17	36	F	161	96	65	129	32	Mild hypertension
18a	45	M	156	88	68	106	50	Postoperative chronic nephritis
24a	44	M	202	104	98	194	8	(End-stage of nephrosclerosis; cardiovascular
24b	44	M	196	94	102	170	26	) disease; renal insufficiency
25	46	M	175	104	71	138	37	Gastric ulcer
29	23	F	174	95	79	153	21	Conversion hysteria
33	48	M	174	102	72	166	8	
34	63	M	194	89	105	152	42	Arteriosclerosis +++
39	57	F	198	100	98	146	52	Menopause
40	63	F	216	101	115	184	32	Arteriosclerosis +
31	54	F	198	91	107	134	64	Moderate arteriosclerosis
42	62	F	209	114	95	165	44	
43	65	F	240	102	138	194	46	Arteriosclerosis ++
47	50	F	154	79	77	119	35	Menopause
48	58	M	167	89	78	147	20	Arteriosclerosis ++
50	60	F	177	107	70	149	28	Arteriosclerosis +
51	52	M	162	71	91	133	29	No arteriosclerosis
52	44	F	180	109	71	165	15	
53	54	F	167	101	67	134	33	Arteriosclerosis ++ and menopause
57	49	F	267	144	123	239	28	Severe hypertension; menopause
63	37	M	173	90	83	131	42	No arteriosclerosis
21	64	F	164	84	80	126	38	
64	53	M	208	109	99	172	36	Severe hypertension; menopause
66	46	M	181	85	96	149	32	Arteriosclerosis ++
67	54	F	150	82	68	121	29	Surgical menopause
68	68	F	220	126	94	165	55	Arteriosclerosis ++
70	60	F	152	87	65	134	18	Arteriosclerosis +
71	56	F	158	78	80	122	36	Auricular fibrillation
72	55	F	171	100	71	160	11	Arteriosclerosis and lymphatic leukemia
73	47	F	190	108	82	153	37	Menopause
79	68	F	194	110	84	193	1	Arteriosclerosis +++
92	60	M	152	86	66	133	19	Bronchial asthma
Averages.....			184	98	86	152	32	
B. Secondary (renal) nephritis (10 patients)								
26a	47	M	207	116	91	144	63	Renal colic
26b	47	M	186	110	76	138	48	Renal colic
30	52	F	225	124	101	210	15	Hydronephritic contracted kidney
44	50	M	197	113	84	172	25	Subacute glomerular nephritis
45a	35	M	195	106	89	169	26	Acute diffuse glomerular nephritis
58a	16	F	163	84	79	130	33	Acute glomerular nephritis
59	67	F	219	98	121	175	44	Arteriosclerosis +
65	38	F	161	94	67	141	20	Chronic pyelonephritis
75	40	F	149	84	65	130	19	Chronic glomerular nephritis
77	27	F	169	97	72	151	18	Acute glomerular nephritis
Averages.....			187	103	85	156	31	
C. Malignant hypertension (9 patients)								
15a	42	M	218	125	93	216	2	Essential hypertension; arteriosclerosis +
15b	42	M	220	120	100	218	2	Essential hypertension; arteriosclerosis +
16	46	F	230	115	115	229	1	Malignant nephrosclerosis; fingers cold and cyanotic
38	29	M	238	135	103	184	54	Malignant hypertension
69	68	F	189	104	85	141	48	Essential hypertension
76	46	F	185	131	54	169	26	Marked retinal changes, postpneumonia; fall in blood pressure
78	48	F	210	141	69	171	39	Early malignant hypertension
46a	60	F	238	102	136	214	24	Coronary sclerosis; convalescent from cystitis
46b	60	F	157	85	72	133	24	Coronary sclerosis; convalescent from cystitis; blood pressure fell after infection
Averages.....			210	118	92	186	24	
Averages of all 3 groups of hypertensive patients..			188	102	86	159	29	

only 1 or 2 mm. below the brachial pressure, a remarkable reduction of pressure gradient. Our fourteen patients with hypotension (table 3) showed an average brachial systolic pressure of 98 mm., an average diastolic pressure of 61 mm. and hence a pulse pressure of 37 mm. The average digital pressure of these patients was 71 mm., which was 27 mm. lower than the brachial systolic pressure.

With this method of determining the digital blood pressure, no diastolic reading can be obtained to compare with the brachial diastolic pressure. It may, however, be of interest to note that, whereas in the controls the average diastolic pressure was found to be approximately half way between the brachial systolic and the brachial diastolic pressure,

TABLE 3.—*Data for Fourteen Hypotensive Patients*

Case No.	Age	Sex	Pressure, Mm. of Mercury: Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial-Digital Gradient	Clinical Diagnosis
7	44	F	103	67	36	74	29	Convalescent from pneumonia
11	45	F	93	56	37	57	36	Ulcerative colitis and arteriosclerosis ++
12	25	F	95	65	30	80	15	Normal
22	25	M	107	68	39	82	25	Arrested pulmonary tuberculosis
32	..	F	99	64	35	89	10	Pleurisy with effusion
35	40	M	102	63	39	59	43	Convalescent from renal cortical abscess
81	58	M	104	50	54	46	58	Emphysema
82	38	M	100	62	38	90	10	Bronchiectasis
84	24	F	84	53	31	59	25	Chronic vaginal fistula
85	39	F	88	54	34	69	19	Convalescent from pyelonephritis
88	55	M	90	58	32	75	15	Coronary heart disease
89	47	M	101	70	31	79	22	Coronary heart disease
90	50	M	99	74	25	71	28	Coronary heart disease
91	33	M	109	55	65	68	41	Chronic ulcerative colitis
Averages.....			98	61	37	71	27	

in the hypertensive patients the average digital systolic pressure rose with the brachial systolic pressure far above the brachial diastolic pressure. For the hypotensive patients the reverse was found to be true, the digital systolic pressure more nearly approaching the brachial diastolic pressure. In fact, in three patients, each of whom had a brachial systolic pressure below 112 mm., the digital systolic pressure actually fell below the brachial diastolic pressure.

These results are summarized graphically in figure 3, where the average pressures obtained for the three groups of hypertensive patients are compared with those for the hypotensive patients and the controls.

It seems certain, therefore, that in hypertension there is no increase in the pressure gradient between brachial and digital arteries; in fact, in cases of very high blood pressure this pressure gradient may even be reduced.

Brachial-Digital Gradient in Paroxysmal Hypertension.—We were fortunate at the time to have a patient with paroxysmal hypertension due to pheochromocytoma. During attacks the patient's face and extremities became cold and blanched, indicating arterial spasm. Large amounts of epinephrine could be demonstrated in the blood during a hypertensive attack but not after operation for removal of the adrenal tumor. The operation also caused a disappearance of the hypertension and effected a complete cure. The complete details of this case are reported elsewhere.[14]

TABLE 4.—*Data for Woman (Case 74) Aged Twenty-Six with Pheochromocytoma*

	Pressure, Mm. of Mercury				
	Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial-Digital Gradient
Before operation					
Resting	184	129	55	141	43
Minutes after exercise: 1	280	190	90	130	150
3	280	160	120	170	110
5	266	158	108	176	90
7	220	148	72	154	66
Resting	192	133	59	165	27
Minutes after exercise: 1	280	180	100	130	150
3	255	160	95	180	75
5	220	150	70	166	54
7	200	140	60	156	44
After operation (removal of pheochromocytoma)					
Resting	133	96	156	90	43

TABLE 5.—*Data for Four Patients with Obliterative Vascular Disease*

			Pressure, Mm. of Mercury					
Case No.	Age	Sex	Brachial Systolic	Brachial Diastolic	Pulse	Digital Systolic	Brachial-Digital Gradient	Clinical Diagnosis
37	52	M	103	65	38	27	76	Thrombo-angiitis obliterans
61	37	F	107	70	37	27	80	Sclerodactylia
80	58	M	104	50	54	29	75	Thrombosis of brachial artery
87	35	F	122	75	47	58	64	Thrombo-angiitis obliterans
Averages			109	65	44	35	74	

It was thought that a patient with this type of disorder would serve as a control for our observations, because it is well known that epinephrine causes constriction of arteries as well as of arterioles. This patient was particularly useful as a control because we were able to make determinations of her blood pressure during attacks of hyper-

14. Beer, E.; King, F. H., and Prinzmetal, M.: Pheochromocytoma with Demonstration of Pressor (Adrenalin) Substance in the Blood Preoperatively During Hypertensive Crises, to be published.

tension due to epinephrinemia and also after restoration of the normal blood pressure by removal of the tumor. It was found that exercise precipitated an attack in this case.

Table 4 demonstrates the results of the two sets of observations: the first, those obtained during paroxysmal hypertension induced by exercise before operation and, later, those of a similar study after operation. It will be seen that during the paroxysmal hypertension induced by exercise the brachial systolic pressure rose to 280 mm. while the digital systolic pressure actually fell from the resting level of 141 mm. to 130 mm. This resulted in a brachial-digital gradient of 150 mm., as contrasted with the 30 mm. gradient of chronic hypertension.

After operation, when the patient's blood pressure returned to a more nearly normal level, the abnormally steep gradient was found to disappear. With a brachial systolic pressure of 133 mm. there was a digital systolic pressure of 90 mm. giving a gradient of only 43 mm.

The fact that for this patient with obvious arterial spasm the pressure gradient became tremendously steep supports our contention that in ordinary hypertension, in which the gradient is either normal or slightly reduced, there is no arterial constriction.

Brachial-Digital Gradient in Obliterative Vascular Disease.—Table 5 shows the readings for four patients with obliterative vascular disease, each of whom had obstruction of the blood flow through the medium-sized arteries. The figures clearly show that the fall in pressure between the brachial and the digital arteries was much greater than in normal persons or in the hypertensive or hypotensive patients. Thus with an average brachial systolic pressure of 109 mm., there was an average digital systolic pressure of only 35 mm., that is, a brachial-digital gradient of 74 mm.

Like the patient with pheochromocytoma, this group of patients showed a marked contrast to our other patients, the data indicating that obstruction of the arteries, whether due to spasm, as in pheochromocytoma, or to organic changes, as in obliterative vascular disease, causes an increased gradient in the fall in pressure between the brachial and the digital artery.

COMMENT

For reasons stated previously, it seems to us that the fact that in ordinary hypertension there is no increase in the brachial-digital gradient must mean that the arteries do not play an important rôle in the production of the high peripheral resistance. The increased resistance must therefore occur in vessels smaller than the digital arteries.

The observation of spasm of the retinal arteries in certain types of hypertension is not incompatible with our results, since the vessels are

considerably smaller than the digital arteries, being more nearly of the order of arterioles.

No apparent relationship was observed between the degree of arteriosclerosis determined by palpation of the radial artery and the brachial-digital gradient, some patients having marked arteriosclerosis and a small gradient and vice versa. This is in agreement with the blood flow previously recorded for persons with thickened radial arteries.[14a]

In the three cases of more serious obliterative vascular disease it is of interest that the digital pressures were all closely alike, being 27, 27, and 29 mm., respectively. Since, according to Landis,[15] this is approximately the same as the normal pressures found on the arterial side of the capillaries, it suggests that it may approximate the lowest pressure at which an adequate capillary flow may be maintained.

It is noteworthy that the patient (case 87) having the least degree of ischemia had the highest digital pressure. These results suggest the possibility that study of the brachial-digital relationship may prove to be a useful index to the degree of obstruction in the arteries.

SUMMARY AND CONCLUSIONS

A study was made of the brachial-digital pressure gradient for subjects with low, normal and high blood pressure.

Similar studies were also made for one patient with paroxysmal hypertension due to adrenal pheochromocytoma and for four patients with obstructive vascular disease.

The average brachial-digital pressure gradient for patients with chronic hypertension was found to be approximately the same as for those with a normal or a low blood pressure. For three patients with a very high blood pressure there was a notable reduction in gradient.

Since there is no increase in the gradient in hypertension, it is concluded that there is no increased resistance in the arteries larger than the digital arteries.

For the patient with pheochromocytoma with epinephrinemia the pressure gradient was markedly increased, indicating constriction of arteries larger than the digital arteries.

For four patients with obliterative vascular disease the pressure gradient was also increased, owing to obstruction in the arteries resulting from organic changes.

This increase in pressure gradient, contrasted with the normal or perhaps decreased gradient of chronic hypertension, supports the view that in hypertension there is no increased resistance in the larger arteries.

15. Landis, E. M.: Capillary Pressure and Capillary Permeability, Physiol. Rev. **14**:404 (July) 1934.

HYDATID DISEASE

CLINICAL, LABORATORY AND ROENTGENOGRAPHIC OBSERVATIONS

M. F. GODFREY, M.D.
SYDNEY, AUSTRALIA

The history of hydatid disease goes back to ancient times. The Jews were familiar with it in their sacrificial slaughter of animals, and the Talmud makes definite reference to it. Hippocrates (460-379 B. C.) wrote of "livers filled with water." References to the disease were made also by Galen (139-200 A. D.) and later by various writers during the Middle Ages, including Rhazes (860-932 A. D.).

At first the condition was considered to be due to morbid processes, such as broken-down lymph glands or collections of pus. Later, however, other investigators brought to light information which led to an understanding of the parasitic nature of Taenia echinococcus. Leuchart, in 1867, described his observations made on artificially infected pigs. However, it was the work of the Italian scientist Francisco Redi (1626-1694) that established the animal origin of the cyst. Thomas, an Australian, published a book in the 1880's. Dévé, of Rouen, France, had compiled a long list of notable contributions that have been made to the literature since his first articles on this subject appeared in 1901. He is regarded as one of the outstanding authorities on this subject today. Dew, an Australian, published a noteworthy book on the subject in 1928.

Weinberg and Ghedini from 1906 to 1909 worked out the complement fixation test. Welsh, Chapman and Storey studied the application of the precipitin test. In 1911 Casoni first used the intradermal reaction to detect hydatid disease. Some time later Keith D. Fairley, N. Hamilton Fairley and Williams, Kellaway, and others carefully investigated the serologic tests for hydatid disease.

During the last seventy years various authors in many countries have written voluminously on the subject, until today the life cycle of the parasite and the clinical and the pathologic aspects of the disease are well understood. Naunyn, of Berlin, Krabbe, of Iceland, and authors from Central Europe and South America also have made valuable contributions on the subject.

DISTRIBUTION

Hydatid disease has been reported from all countries, and, though the disease has a universal distribution, it is found chiefly in countries

where sheep are raised, the sheep being the usual intermediary host. One of the factors necessary for the infestation of a country is that dogs have access to sheep's organs. In Australia and New Zealand, where there are roughly 13 and 15 sheep, respectively, per capita, the viscera of slaughtered sheep are frequently fed to dogs.

In Iceland, where there are approximately 2 sheep per capita and many dogs are kept to handle the sheep, Krabbe [1] found that 28 per cent of the dogs were infected; another writer there found that 1 of every 6 persons who came to autopsy was a victim of the infection. More recently the people of Iceland have been educated as to the dangers of the disease, and there has resulted a marked decrease in the rate of infection, so that in 1920 Sambon [2] found that the incidence was 1 in every 2,000 of the population, where formerly it had been 1 in every 40.

Other countries showing hydatid infection commonly are Algiers, Bulgaria, Roumania, certain parts of Switzerland, France, Austria, Serbia, northern Italy and Russia.

In North America, where there is 1 sheep to every 3 persons, the incidence among human beings is low. In a series of 241 reports of cases collected by Lyons [3] in the United States and Canada, it was found that 91 per cent of the cases comprising the series were those of patients of foreign extraction. Osler,[4] in a paper published in 1882, reported 66 cases of hydatid disease in human beings but stated that he was unable to find a single case of Taenia echinococcus infection in dogs.

During the last four decades an increasing number of sheep have been raised in the republics of Argentina and Uruguay, and this has been associated with a great increase in the incidence of hydatid infection in human beings there. According to Carbonell and Zwanck, the infestation in some parts of those countries has risen to 50 per cent of the populace. In Argentina Greenway reported that between 1910 and 1921 the incidence of hydatid infection increased at twice the rate of the increase in the population. This great increase in the incidence is due to the ignorance of the peons, their primitive method of living and the infection of water supplies.

---

1. Krabbe, H.: Recherches helminthologiques en Danemark et en Islande, Copenhagen, G. E. C. Gad, 1866, p. 3.

2. Sambon, L. W.: Researches on Epidemiology of Cancer Made in Iceland and Italy, J. Trop. Med. **28**:39 (Feb. 2) 1925.

3. Lyons, I. P.: The Incidence of Hydatid Disease in North America, Am. J. M. Sc. **123**:124, 1902.

4. Osler, W.: On Echinococcus Disease in America, Am. J. M. Sc. **84**:475, 1882.

For Australia Thomas [5] recorded a twenty year period: During the first five year period there were 57 cases; during the second period, 112 cases; during the third period, 192 cases, and during the fourth period, which led up to 1882, 231 cases. The greatest incidence of the disease was in the southwest portion of Victoria, which has a climate not unlike that of Colorado. The incidence of the disease among Victorian hospital patients has been placed by Dew [6] at from 1 to 294. This survey covered a period of nine years.

One thousand miles to the north of Victoria lies the State of Queensland, with its semitropical and tropical climates. Sheep raising is not so extensively carried on in Queensland as in Victoria, and the incidence of hydatid infection is lower there than in Victoria. This is due in part to the warmer climate of Queensland. The echinococcus parasite is killed by a temperature of 50 C., which frequently obtains during the summer months in some parts of Queensland.

It is of interest to note here the high incidence of infection in Australian sheep, as found by Ross in a survey made in New South Wales in 1926, when he discovered that in small abattoirs in the country 35.7 per cent of sheep slaughtered were infested with hydatid disease.[7]

LIFE CYCLE

The life cycle of Taenia echinococcus has been well described by various workers and therefore will be dealt with only briefly. In this infection a human being is only accidentally the intermediary host and represents a blind pocket so far as the further dissemination of the organism is concerned. The dog, wolf and jackal are the ideal definitive hosts, and they infect the food and the water supply of the herbivorous animals by fecal contamination.

The development of the parasite in man is considered to be identical with that in sheep and other intermediary hosts. Cattle are more commonly infected than sheep but are not a source of infection to dogs, for the reason that dogs are more frequently fed the viscera of sheep.

The ovum as passed by the dog is composed of a hard, striated capsule containing a hexacanth embryo. When swallowed by man, sheep, ox or pig, this ovum hatches out in the stomach or duodenum. The embryo escapes and bores its way through the wall of the stomach;

5. Thomas, J. D.: Hydatid Disease, London, Baillière, Tindall & Cox, 1894, p. 149.

6. Dew, Harold R.: Hydatid Disease, Sydney, Australasian Medical Publishing Company, Ltd., 1928, p. 43.

7. Fairley, N. Hamilton, and Penrose, J. S.: A Survey of the Incidence of Hydatid Disease in the Herbivora and Porcines of Victoria, M. J. Australia **2**:640 (Nov. 24) 1928.

then, entering the radicles of the portal vein, it is swept into the liver, where in the majority of cases it lodges in the lobules. After it has lodged in the liver, it may be destroyed by the reaction of antibodies. If it survives, it becomes surrounded by small mononuclear cells. After seventy-two hours eosinophil and endothelial cells appear. Dew [6] stated that after fourteen days vesiculation occurs and the chromatin of the parasite becomes arranged in nuclear masses. Hyaline changes then take place in the cytoplasm, and fluid forms in the center of the cellular mass. At the end of three weeks the cystic follicle is visible with the unaided eye, and by the end of five months it has developed into a cyst with a diameter of 1 cm. The cyst may continue to grow, reaching a capacity as great as that of Barnett's "colossal hydatid cyst of the abdomen," from which he removed 11 gallons (42 liters) of hydatid fluid; [8] or it may retrogress, the laminated membrane becoming wrinkled and calcareous changes frequently taking place.

The wall of the cyst is formed of two layers, ectocyst and endocyst, in addition to a protective fibrous pericyst, called the adventitia. The adventitia is formed by the tissues of the host. The germinal layer, or endocyst, produces numerous brood capsules, which are attached to it by a fine pedicle and float in the fluid contained in the cyst. Within the brood capsule the scolices, or heads of the future worms, develop. A scolex is an oval body just visible with the unaided eye. This head segment of the future worm contains two rows of hooklets. In addition, there are four suckers in the head of the fully developed worm. As a result of trauma, such as needling or a blow, which threatens the vitality of the cyst, daughter cysts develop in the germinal membrane. The daughter cysts contain both scolices and brood capsules, like the mother or original cyst.

When the cyst containing viable scolices is ingested by the definitive host (dog, wolf or jackal), the scolices become attached to the walls of the small intestine and develop into complete worms, having three or four segments. The parasite measures about 5 mm. in length. It lies parallel to, and is about the same size as, the villi of the small intestine. The terminal segment, containing the ova, eventually ruptures, freeing scores of ova; and it is in this way that the feces of the dog contaminate the pastures and the water supply of the herbivora.

Dévé [9] has shown that the ova resist prolonged drying as well as soaking in water. But the period of the viability of the ova and the extremes of temperature it will withstand are not fully known.

---

8. Carmalt-Jones, D. W.: Hydatid Disease as a Clinical Problem, Brit. M. J. **2**:5 (July 6) 1929.

9. Dévé, F.: Echinococcose primitive expérimentale; kystes hydatiques de la plèvre, Compt. rend. Soc. de biol. **64**:587, 1908.

Sir Louis Barnett[10] stated the opinion that human infestation from dogs occurs more frequently through the handling of dogs than from the feeding of dogs from plates, the cause given by Baring-Gould[11] for the infestation in Iceland.

INCIDENCE IN VARIOUS ORGANS

In man the presence of one or more cysts in some part of the body constitutes hydatid disease. The usual site of involvement is the liver, from which the peritoneum is secondarily involved. After this in frequency come the lung, muscles and cellular tissues, kidney, spleen, bones, orbit and brain.

The cases on record in the registry for hydatid disease of the Royal Australasian College of Surgeons up to the beginning of the year 1935 showed the location of cysts and the mortality to be as follows:[10]

Site	Cases	Deaths
Liver	240	45
Other abdominal organs, mostly secondary to cysts in the liver	50	7
Lung	74	12
Muscles and fascia	21	1
Bone	14	1
Kidney	11	2
Brain	5	2
Spleen	2	1
Thyroid gland	2	..
Total	428	71 (16.6%)

Dévé (quoted by Carmalt-Jones[8]) gave the following distribution for two thousand, seven hundred and twenty-seven cysts:

Sites	Percentage
Liver	76.6
Lung	9.4
Muscles and cellular tissues	5.2
Kidney	2.3
Spleen	2.1
Bones	0.9
Orbit	0.2
Brain	0.6
Miscellaneous	2.2

The following figures bear out the relatively high frequency of cysts in the liver: Dévé, 76.6 per cent; Fairley,[12] 72.9 per cent, and MacLaurin,[13] 74 per cent.

DIAGNOSIS AND LABORATORY TESTS

The only symptom of hydatid disease, as long as the cyst is intact and uninfected, may be dyspnea or a slowly growing painless tumor of

10. Barnett, L. E.: Deaths from Hydatid Disease, Australian & New Zealand J. Surg. **5**:205 (Jan.) 1936.

11. Baring-Gould, S.: Iceland, Its Scenes and Sagas, London, Smith Elder & Co., 1863, p. 58.

12. Fairley, K. D.: Hydatid Disease of Liver, M. J. Australia **1**:177 (Feb. 23) 1924.

13. MacLaurin, C.: The Symptoms of Liver Hydatid, Australasian M. Gaz. **28**:295 (June 21) 1909.

the abdomen. But should rupture or leakage occur, anaphylaxis follows, the most usual form being hydatid rash with urticarial wheals. Frequently accompanying these are irregular fever, dyspnea, cyanosis, vomiting, abdominal pain, syncope, delirium and mania. In the event that a quantity of hydatid material suddenly enters the blood stream, serious anaphylactic symptoms or even sudden death may result.

Dew [6] has listed the symptoms of anaphylaxis according to systems as follows:

Cutaneous: Pruritus, urticarial wheals, erythema and sweating

Gastro-intestinal: Nausea, vomiting, diarrhea, tenesmus, abdominal pain and melena

Respiratory: Tightness in the chest, spasmodic asthmatic cough, dyspnea, cyanosis, pulmonary edema and edema of the glottis

Cardiovascular: Pallor, faintness, tachycardia, clammy skin, cold extremities, syncope and collapse

Nervous: Agitation, convulsions, dilated pupil, delirium and coma

Previous to the advent of modern serologic and roentgenographic methods, correct diagnoses were made in about 40 per cent of cases. With the use of modern laboratory methods the percentage has risen to about 90. Three laboratory tests are of great value:

1. The precipitin test: This test, which employs the serum of the patient in prepared hydatid fluid, is accurate in 65 per cent of cases. It is of value only when used with carefully prepared controls.

2. The intradermal test: The intradermal test of Casoni is very valuable. It is carried out in a manner similar to that of the Pirquet test for tuberculosis. Hydatid fluid obtained by puncture of an aseptic cyst from the lung or liver of a sheep is filtered and used for this test. When 0.3 cc. of the fluid is injected intradermally into the arm of the patient, a wheal is raised that is about 8 mm. in diameter. An injection of physiologic solution of sodium chloride should be used as a control. When the reaction is positive, the wheal reaches its maximum size of 4 or 5 cm. in from ten to twenty minutes and is surrounded by an erythematous zone. This test, according to Fairley,[14] showed positive results in 56 per cent of the cases in which there were uncomplicated cysts and in 26 per cent of the cases in which there were ruptured or suppurating cysts. The Casoni test is a useful preoperative guide, since it indicates when there has been a dangerous degree of absorption of hydatid fluid.

3. The complement fixation test: This test is specific and is dependent on a specific antibody in the serum of patients who have

14. Fairley, K. D.: The Intra-Dermal Test in Hydatid Disease: A Clinical Analysis of Its Results, M. J. Australia **1**:472 (April 13) 1929.

absorbed hydatid antigen. Fairley's technic is similar to that of the Wassermann test. According to Fairley and Williams,[15] in 52.4 per cent of cases there is a positive reaction preoperatively; whereas in 52.8 per cent of cases there is a positive result when there are residual or recurrent cysts.

Leukocyte Count.—When the common causes of eosinophilia, such as asthma, chronic disease of the skin and intestinal worms can be eliminated, a certain amount of reliance may be placed on the presence of eosinophilia. In about half the cases of hydatid disease the eosinophil count is higher than normal, the upper limit of normal being placed by Fairley and Kellaway[16] at 300 eosinophilic leukocytes per cubic millimeter of blood (6 per cent). Rarely, the eosinophils outnumber the neutrophils.

CHARACTERISTICS OF HYDATID ELEMENTS

The hydatid fluid is clear, limpid and alkaline, with a specific gravity of from 1.008 to 1.015. It contains about 6 per cent of sodium chloride. After centrifugation it should be examined for scolices and hooklets. A scolex measures 160 microns in length and 115 in breadth. Hooklets also may be seen, their length varying from 20 to 40 microns.

ROENTGENOGRAPHY

The roentgenographic diagnosis of hydatid disease has certain limitations as well as a wide range of usefulness. As in some other diseases, it is frequently necessary to place considerable weight on the clinical and other laboratory findings before the roentgenograms can be properly interpreted. Modern roentgenographic and serologic methods used together make diagnosis possible in 90 per cent of cases.

The problem of properly evaluating roentgenograms is variable, as different parts of the body are involved. Perhaps it would be well to consider briefly the causes of the shadows under question. The classic cyst has a wall composed of three layers: adventitia, ectocyst and endocyst.

The adventitia, which is the pericyst, or outer layer, is made up of tissues derived from the host. In some organs, such as the liver, it may be dense and capable of casting a definite shadow; in other tissues, such as the lung, it may be so thin as not to cast a shadow. Again, a

15. Fairley, K. D., and Williams, F. E.: The Complement Fixation Test in Hydatid Disease: An Analysis of Its Results, J. Coll. Surgeons, Australasia **2**:317 (March) 1930.

16. Fairley, K. D., and Kellaway, C. H.: The Value of Laboratory Investigations in the Diagnosis of Hydatid Infestation, Australian & New Zealand J. Surg. **2**:236 (Jan.) 1933.

living cyst in the abdomen, for instance, may or may not cast a shadow; but should death of the cyst occur, calcium would be laid down in the adventitia, making the cyst visible.

The ectocyst and its fluid contents cast a shadow, as would any localized collection of fluid.

The endocyst is a fragile nucleated germinal layer lining the interior of the laminated layer. It casts no roentgenographic shadow.

The roentgenographic appearance of hydatid cysts in various parts of the body will now be considered in the order of the frequency of involvement.

LIVER

According to Dévé, 76.6 per cent of all hydatid cysts are located in the liver. They grow silently for years, causing the patient little or no discomfort. In size they vary from that of a small pea up to that of a tennis ball. Rarely, a cyst of "colossal" size has been recorded. At times, however, the cyst may become infected and suppurate, or it may rupture into the peritoneal cavity, with widespread dissemination of brood capsules and other hydatid elements. Again, the cyst may rupture into a biliary channel, either within or without the substance of the liver, or into the gallbladder. Another common occurrence is transdiaphragmatic rupture, with emptying of the contents of the cyst into the pleural space or into a bronchus.

According to MacLaurin,[13] in 80 per cent of cases there is involvement of only the right lobe of the liver, in 18 per cent there is involvement of the left lobe only and in 2 per cent there is involvement of both lobes. This is probably due to the fact that the right hepatic vein has a larger lumen and runs a straighter course than the left hepatic vein. This was observed by Castex, who studied the vascular system of the liver roentgenographically after the injection of opaque material into the portal vein.

Dew [6] has stated that approximately 75 per cent of all cysts of the liver are situated either antero-inferiorly or postero-inferiorly, so that they have a tendency to extend downward into the abdominal cavity. This is of clinical importance, as the tumor is frequently rounded, cystic, smooth and not tender and moves freely with respiration. The hydatid "thrill," according to Carmalt-Jones,[8] was noted in only 7 of over 300 cases by Barnett.

The principle roentgenographic sign of hepatic involvement is elevation of the right dome of the diaphragm, with disturbance of its normal contour. Frequently the altered contour shows segmentation. This may be due to the presence of one or more hepatic cysts in or near the upper surface of the liver, or again it may be due to compensatory hypertrophy of the hepatic cells overlying a cyst. The diaphragm

may be elevated 2 or 3 inches (5 to 8 cm.). Fluoroscopic examination usually reveals diminution of the diaphragmatic excursion. If there is an infected cyst near the upper surface of the liver, there may be loss of definition of the overlying portion of the diaphragm, owing to inflammation.

Roentgenographically it is frequently difficult or impossible to demonstrate cysts deep in the liver or hanging from its inferior surface. Some cysts growing on or projecting from the inferior surface of the liver can be demonstrated by means of a barium sulfate meal or enema, cholecystography or pyelography.

For localization of hepatic hydatid cysts, it is suggested that stereoscopic films, with Claessen's heavy penetration, as for the spine, be used. I have used stereoscopic films with good localization when there were broken-down calcified cysts and heavy penetration was unnecessary.

Claessen [17] has stated that in Iceland some calcification of the pericyst is noted in a fair percentage of cases and that by using the same penetration as for the spine the early calcification of a living cyst can be delineated. The female breast sometimes casts a confusing semicircular shadow. Anderson [18] has stated that the perihilar basal markings of the lungs extending up from the area of involved liver are increased in density. He stated that this may be due to changes in the lymphatic radicles.

Differential Diagnosis.—Conditions which must be considered are hepatic abscess, malignant growth, cirrhosis, syphilis and diaphragmatic adhesions.

Hepatic Abscess: Usually there is adequate clinical support, and the serologic findings are normal. Analysis of the stools may reveal Endamoeba histolytica.

Malignant Growth: The outline of the tumor is not sharply defined or regular in contour. Jaundice may be present. A primary neoplasm may be discovered in the stomach or elsewhere. Serologic findings are normal.

Portal Cirrhosis: This can usually be diagnosed clinically and, from the laboratory standpoint, without difficulty. Jaundice occurs in 35 per cent of cases. The spleen is enlarged in 80 per cent of cases. Hematemesis occurs in 25 per cent of all cases of cirrhosis and is an early symptom. Serologic tests give negative results.

17. Claessen, G.: The Roentgen Diagnosis of Echinococcus Tumors, Acta radiol., supp. 6, 1928.

18. Anderson, C. C.: Difficulties and Fallacies in the Radiological Diagnosis of Hydatid Infection, J. Coll. Surgeons, Australasia **2**:301 (March) 1930.

Syphilis: In cases of hereditary syphilis there are the well known signs of the disease. In cases of acquired syphilis the Wassermann reaction is positive, and the irregularities on the anterior surface of the liver due to gummas rapidly disappear under antisyphilitic therapy.

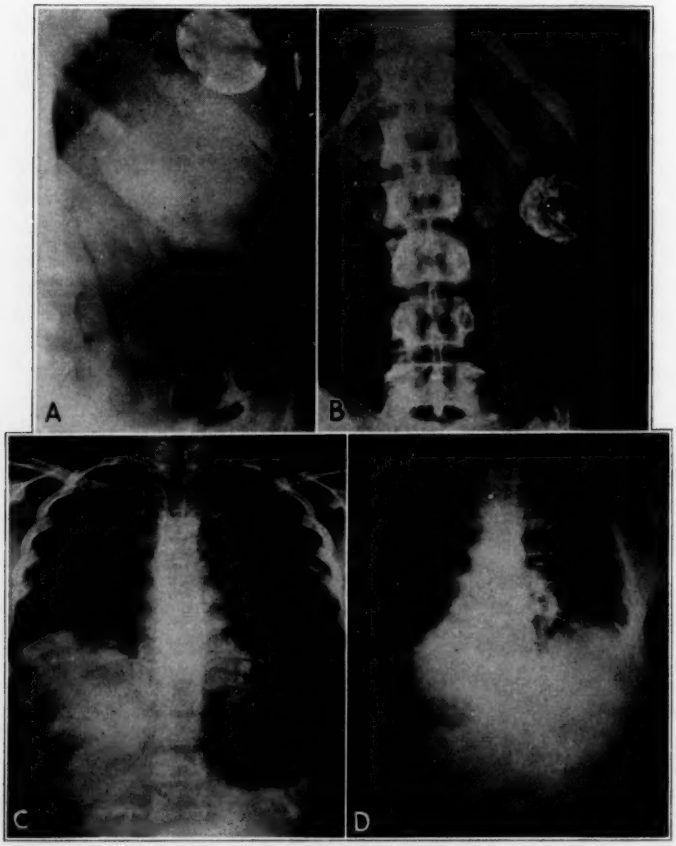


Fig. 1.—*A*, roentgenogram of an infected cyst of the right lobe of the liver with calcification of the pericyst. *B*, a large cyst extending from the antero-inferior surface of the liver, showing calcification of its capsule. *C*, a large cyst occupying the right lobe of the liver, with marked elevation of the diaphragm and irregular segmentation of its contour. *D*, a cyst involving the right lobe of the liver, with marked elevation of the diaphragm. Note the increased density of the perihilar basal shadows on the right side, which are described by Anderson as probably representing changes in the lymphatic radicles.

The intradermal test may or may not give positive results and is occasionally unreliable, according to Fairley, Fairley and Williams.[19]

Diaphragmatic Adhesions: These usually present an irregular breaking up of the dome of the diaphragm, due to "peaking" or "tenting," and questioning may reveal an old history of basal pleurisy or pneumonia. Serologic tests give negative results.

Surgical Treatment.—The surgical treatment of hepatic cysts is not within the purview of this short paper, and for this the reader is referred to the subject as outlined by Harold Dew.

LUNG

Hydatid disease of the lung occurs in 12.5 per cent of cases. In the lung the cyst may be either primary or secondary. The primary cyst

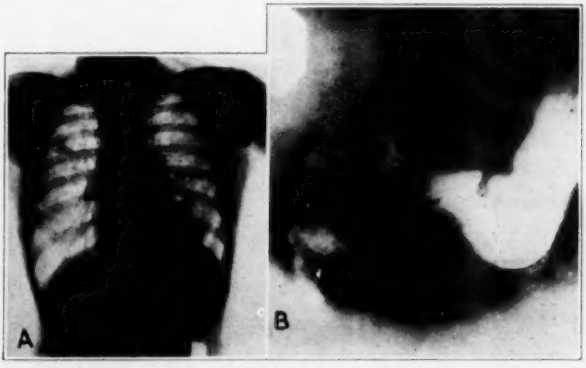


Fig. 2.—*A*, calcification of the adventitia of two collapsed cysts involving both the right and the left lobe of the liver. *B*, a large cyst involving the left lobe of the liver and extending from its lower surface. Note the calcification in the pericyst and its close relation to the lesser curvature of the stomach. Also note the size of the cyst.

is derived from a hexacanth embryo and is carried to the lung. This type is the more frequent. The secondary type develops from brood capsules or scolices.

In cases of pulmonary cysts the distribution is roughly 65 per cent in the right lung and 35 per cent in the left lung, with a special predilection for the base of the right lung. In the lung the adventitia is relatively thin; consequently these cysts rarely become old. As they expand a

19. Fairley, Keith D.; Fairley, N. Hamilton, and Williams, F. Eleanor: Some Fallacies in the Intra-Dermal Test for Hydatid Disease, M. J. Australia **2**:320 (Sept. 7) 1929.

small bronchus may become included in the pericystic coat and may become occluded. However, the bronchial epithelium is more resistant to fibrosis, and later the patent bronchus may open into the cystic cavity, permitting extravasation of the germinal membrane and brood capsules, as well as the grapelike daughter cysts, which are sometimes present and which may be coughed up. Expansion of the cyst usually is more marked toward the pleural surface of the lung, so that in time these cysts frequently lie just beneath the pleura. In some cases the diagnosis is rendered difficult because of the presence of free pleural fluid, and it may be necessary for the pleurisy to resolve before the condition can be diagnosed.

When a pulmonary cyst breaks down it may rupture into a bronchus, or, particularly if it lies in a subpleural position, it may rupture into the pleural space. When it ruptures into a bronchus there is usually a rush of salty-tasting clear fluid into the mouth, and if the cyst contains daughter cysts, the patient coughs up "something that looks like grape skins."

When deeply placed parabronchial cysts rupture, the possibility of spontaneous recovery is good. Lepicard [20] and Bellard [21] have stated that in from 80 to 90 per cent of these cases natural cure results.

In cases of subpleural cysts the chances of spontaneous cure are not so promising, and early surgical treatment is required either before or after rupture. The typical cyst is slightly ovoid or elliptic, though it may be circular.

The more frequent location of the pulmonary cyst is in a subpleural position. If it is flattened on one side, it is usually at the place of contact with the wall of the chest or with the diaphragm and liver. The adventitial layer of the wall of these cysts is frequently thin, as they rarely become old; hence the only roentgenographic finding may be a cystic area filled with fluid. If only one cyst exists, it is more frequently found posteriorly at the base of one lung; whereas if several cysts are present, according to Anderson,[22] the greater portion of one or both lungs may be displaced.

When the cyst communicates with a bronchus, the foul sputum may simulate that of bronchiectasis. Brailsford [23] suggested that iodized poppy-seed oil 40 per cent be used to demonstrate these cavities.

---

20. Lepicard, S.: La vomique hydatique pulmonaire, Thèse de Paris, no. 290, 1912.

21. Bellard, L.: Contribution à l'étude de la vomique, hydatique curative, Thèse de Paris, no. 105, 1924.

22. Anderson, C. C.: Radiological Diagnosis of Hydatid Infection, Brit. J. Radiol. **1**:428 (Nov.) 1928.

23. Brailsford, James F.: Hydatid Disease in England, Brit. M. J. **1**:133 (Jan. 24) 1931.

Köhler,[24] in discussing large circular shadows in the lung, stated that they may be produced by echinococcosis, carcinoma, sarcoma, abscess, interlobar empyema, actinomycosis, infarct and intrathoracic struma. It is well to include dermoid cysts in this list. These conditions will now be briefly considered separately.

Differential Diagnosis.—Carcinoma: Carcinomatous tumors are usually multiple, the growth is more rapid than that of a hydatid cyst and the outline of the metastases is not so sharply defined as that of a hydatid cyst. Usually it is possible to demonstrate a primary growth, and there is considerable cachexia. No eosinophilia is present. Serologic examination reveals no abnormality.

Fig. 3.—A case of apparently spontaneous cure. The patient, a man aged 55, stated that ten years previously he coughed up "about 500 grape skins" and was in poor health. He now is in excellent health and weighs 45 pounds (20.5 Kg.) more than he did ten years ago. A Casoni test was recently performed and gave a negative result. At present there is little excursion of the left dome of the diaphragm, and much fibrosis is present at the base of the left lung.

Sarcoma: A primary growth may be demonstrable, and cachexia may be present. Bull [25] stated that the edges fade into the surrounding pulmonary tissues, giving much the same picture as seen in the earliest stages of pulmonary abscess. However, some round, "cannon-ball" sarcomatous deposits are sharply defined at the periphery and show a

24. Köhler, A.: Röntgenology, ed. 2, London, Baillière, Tindall & Cox, 1935, p. 385.

25. Bull, H. Cecil H.: X-Ray Interpretation, London, Oxford University Press, 1935, p. 316.

greater density than a hydatid cyst. No eosinophilia is present. Serologic examination reveals no abnormality.

Abscess: Abscess may follow tonsillectomy or infection from a known focus. There is a septic type of temperature curve. No eosinophilia is noted. Serologic tests give negative results.

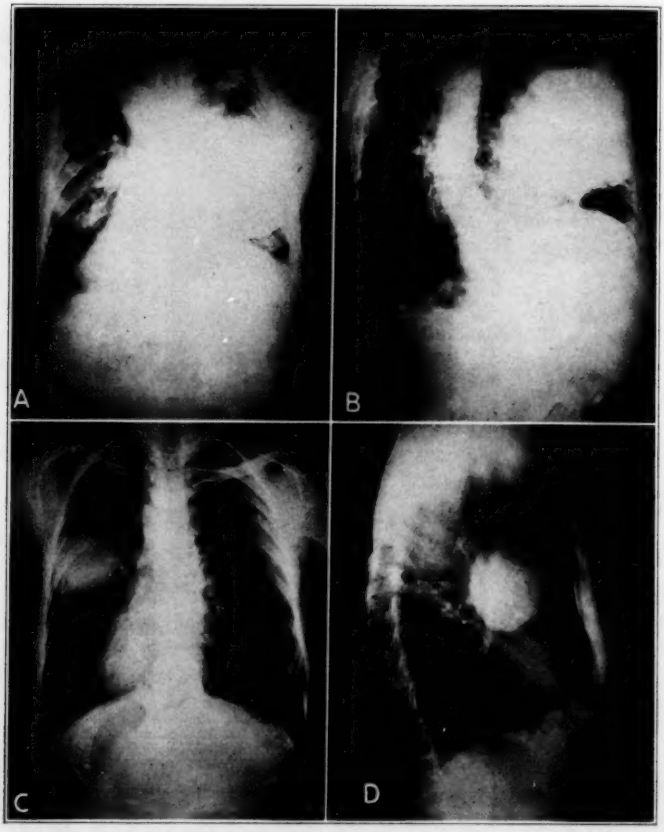


Fig. 4.—*A*, a large cyst filled with fluid, occupying the midportion of the right lung. There is also considerable elevation of the right dome of the diaphragm, owing to the presence of a cyst in the right lobe of the liver. *B*, an oblique view of the same patient as shown in *A*. Note the anterior position of the cyst in the lung and the density of the cyst as compared with the shadow caused by the heart. The loss of definition of the cysts speaks for infection and inflammatory changes. *C*, a cyst occupying the midportion of the left lung. Note its flattened lateral surface. *D*, a lateral view of the same patient as shown in *C*.

Interlobar Empyema: Frequently interlobar empyema follows pneumonic consolidation. There is a septic type of temperature curve, and other findings are similar to those noted in cases of pulmonary abscess.

Actinomycosis: Actinomycosis is due to the Streptothrix organism. Pleural adhesion usually develops, but occasionally empyema results. This disease spreads by contiguity through all the tissues. When a subcutaneous abscess ruptures or opens, granules of sulfur may be found. The clinical findings are similar to those in pulmonary tuberculosis. Serologic tests give negative results.

Infarct: After the formation of a thrombus in the heart, which may be associated with coronary occlusion, an infarct may develop. No eosinophilia is noted, and serologic tests give negative results.

Intrathoracic Struma: Frequently intrathoracic struma is associated with dysphagia and dyspnea; rarely is cardiac embarrassment noted. There may be hyperthyroidism. No eosinophilia is present. Serologic tests give negative results.

Dermoid Cysts: Dermoid cysts are easily distinguishable roentgenographically because of the contents, such as teeth or ossicles. Growth is very slow. Sometimes a dermoid cyst shows a changing fluid level when the patient alters his position.[26]

KIDNEY

Hydatid disease of the kidney is rare (2.3 per cent, Dévé), because of the difficulty for the hexacanth embryo to pass through both the hepatic and the pulmonary filter. When it does occur it may involve either the perirenal or the parenchymal tissue, in the latter case causing pressure atrophy of the renal substance. In the majority of cases the cyst ruptures into the renal pelvis and drainage results, but eventually stagnation of the urine occurs, disposing toward pyelitis and pyelonephritis. Occasionally, previous to rupture the cyst may encroach on the ureter or on one of the major calices, resulting in hydronephrosis. At times, after the breakdown of the cyst, the cystic wall or other hydatid elements become impacted in the ureter. This is followed by renal pain and colic. The pain may be intermittent or persistent and has been known to last for years. During these attacks, hematuria may be present, and the urine may contain hydatid membrane, scolices, daughter cysts or hydatid fluid.

---

26. Phemister, Dallas B.; Stenn, William B., and Volderaner, John C.: A Roentgenologic Criterion of Dermoid Cyst, Am. J. Roentgenol. **36**:14 (July) 1936.

Dew [6] has listed the following indications for nephrectomy:

1. Conversion of the whole organ into a cystic mass, the kidney appearing as a mere appendage to the cyst
2. Multiple cysts of the kidney, when conservative measures would be difficult or impossible
3. Complications, such as existent calculi, pyonephrosis or infection confined to the kidney
4. Fistulous communications with the intestines
5. Complications during operation, such as hemorrhage or contamination of the area

Cysts of the kidney have no distinctive roentgenographic appearance. A barium sulfate enema may aid in localizing the cyst. The serologic tests give positive results. The finding of a hydatid membrane, scolices or hooklets in the urine makes the diagnosis positive.

Differential Diagnosis.—Hypernephroma: Hypernephroma is characterized by an insidious development, hematuria, no eosinophilia and negative results of serologic tests.

Paravertebral Abscess: Paravertebral abscess is associated with Pott's disease of the spine.

SPLEEN

The spleen is involved in about 2 per cent of cases. The cyst is usually primary, in that the hexacanth embryo is carried to it by way of the blood stream. A cyst of the spleen is usually single and may reach enormous proportions. In a case recorded by Wilson [27] the cyst reached into the bony pelvis. Pain is usually dull, and frequently there is a feeling of heaviness in the upper portion of the abdomen. At times there are nausea and vomiting. Clinically there may be bulging of the ribs, as well as an epigastric mass below the left costal margin. As stated previously, on rupture of a splenic cyst, hydatidosis frequently results. In cases in which the cysts are multiple, a cardiac origin should be suspected.

The treatment advocated is splenectomy, since it offers a possibility of complete removal of the parasite and causes only passing changes in the nature of the elements of the blood.

Roentgenographically the barium meal may reveal distortion of the greater curvature of the stomach, and a pyelogram may assist in differentiating renal conditions.

Differential Diagnosis.—This includes a consideration of the Grawitz tumor and hydronephrosis. These can easily be eliminated by laboratory methods.

---

27. Wilson, T. G.: A Case of Hydatid Cyst in the Spleen Simulating an Ovarian Cyst, J. Obst. & Gynaec. Brit. Emp. **7**:413, 1905.

BONE

The diagnosis of hydatid infection of the bone is difficult. This condition occurs in only 0.9 per cent of cases of hydatid infection, according to Dévé. A peculiarity of this condition is that there is no adventitia. In fact, the fibrous tissue usually laid down by the host is absent, and the outer surface of the cyst contains numerous osteoclasts. In the long bones the most helpful diagnostic finding is a burrowing multilocular growth which invades and destroys the bone and leaves a chain of "punched-out appearing areas" of decreased density. Periosteal reaction is lacking until the cortex is broken through.

Fig. 5.—A large partially calcified cyst occupies the upper pole of the enlarged spleen. Note its relation to the upper part of the stomach.

At other times the multilocular appearance of the area involved closely simulates that of a giant cell tumor. The organism extends along the haversian canals, and occlusion of the small arteries occurs. This permits necrosis of the bone, with the occasional formation of cavities containing hydatid cysts.

If the periosteum is involved, it reacts only feebly and is violated early. After reaching the soft tissues, the parasite shows the typical univesicular type of growth, with the formation of a fibrous adventitia. The end of hydatid disease of all long bones is pathologic fracture, which practically never heals. The serious import of this condition in bone makes complete excision of the infected area imperative. Incision, curettage and treatment with formaldehyde are unsatisfactory. A bone

graft should be inserted after the diseased bone has been removed. In cases in which the soft tissues also have been involved, amputation above the area involved is the method of choice. Roentgen treatment has not proved satisfactory, according to Dévé, Billiard and Decoularé-Delafontaine.[28]

Involvement of various flat bones has been recorded, the ilium being most frequently affected. This condition is characterized by slowly growing, painless, fluctuant, nodular swelling. Limitation of movement follows involvement of the acetabulum. Late in the condition there may be irritation of the lumbosacral nerves.

In flat bones the roentgenogram shows closely packed cystic involvement of the bone; the cysts are separated by coarse trabeculae, and the cancellous structure of the bone is distorted, appearing burrowed and expanded. The cortex may be irregularly thickened, owing to osteoblastic reaction, and a multilocular appearance may result. Small islands of calcium may be seen scattered throughout the diseased cystic area.

Differential Diagnosis.—Hydatid disease of bone must be differentiated from carcinomatous and sarcomatous deposits, enchondroma and endosteal sarcoma, as well as fibrocystic disease and myeloma.

The entire absence of actual bony reaction is helpful in diagnosing hydatid disease. Hydatid cysts of bone are usually unrecognized until late.

Brailsford [29] described a case of hydatid disease of the mediastinum in which treatment for tuberculous abscess was given in a sanatorium. Eventually the vertebrae were involved.

BRAIN

Involvement of the brain occurs in 0.6 per cent of cases and may be either primary or secondary. The primary form, as in the case of the kidney, is derived from a hexacanth embryo and is carried by the blood stream. This type is more frequently found in children. The cysts are usually single. The secondary form is derived from hydatid elements and is frequently multiple. It is usually found in adults. Manifestations of the two types are quite different.

Primary cysts are at least seven times as frequently found in children less than 15 years of age as in adults. Owing to the impossibility of expansion, hydatid cysts of the brain give rise to serious symptoms before they have assumed large proportions. Therefore, children suffering from this condition usually do not reach adult life.

---

28. Dévé, F.; Billiard, A., and Decoularé-Delafontaine, A.: Sable hydatique et radiothérapie pénétrante, Compt. rend. Soc. de biol. **91**:1365 (Déc. 20) 1924.

29. Brailsford, J. F.: Diseases of the Hip-Joint and Its Immediate Neighbourhood, Brit. M. J. **1**:92 (Jan. 16) 1932.

In the primary type of involvement there is increased intracranial pressure, usually associated with increased pressure of the cerebrospinal fluid. Owing to this increased intracranial pressure, molding and thinning of the bones of the skull and osteoporosis may occur. According to Dew,[30] this may be so pronounced that palpation over the area may

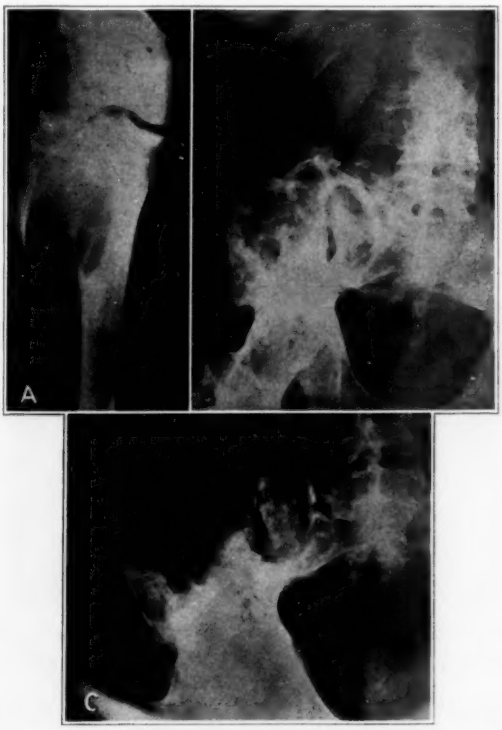


Fig. 6.—*A*, hydatid disease involving the upper fourth of the tibia. Note the expansion of the cortex, the displacement of the fibula and the resemblance to giant cell tumor. *B*, hydatid disease of the crest and body of the ilium. Note the appearance of burrowing, with irregular cavitation and destruction of the architecture of the bone. Also note the ankylosis of the hip joint following involvement of the acetabulum. *C*, a similar type of case to that shown in *B*. Again note the ankylosis of the hip joint.

elicit crackling or pressure may cause indentation. Headache is common, and there may be jacksonian epileptiform seizures, which are sometimes followed by paralysis.

30. Dew,[6] p. 359.

Differential Diagnosis.—This is difficult, since different neoplastic conditions give rise to confusing neurologic symptoms. Aspiration of the cystic contents is perilous. If the cyst is primary, operation should be performed as soon as possible. If multiple cysts are present, the condition is hopeless, and death from pressure is usually not long delayed.

PERITONEUM AND PELVIS

Involvement of the peritoneum or pelvis usually comes about in one of two ways; first, by extrusion of an intact simple cyst from the liver or spleen and, second, by rupture of a cyst in the liver or spleen, with spilling of the hydatid elements over the peritoneal surfaces.

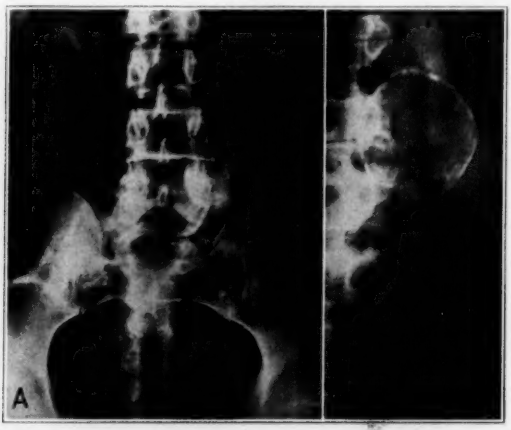


Fig. 7.—*A*, one large and several small hydatid cysts attached to the omentum. *B*, a large omental cyst situated just below and pressing on the dye-filled gallbladder.

Dew [31] called the latter catastrophy hydatidosis; it represents the sowing and survival of numerous hydatid elements. In the female the elements are prone to lodge in the pouch of Douglas. Either a vaginal or a rectal examination will aid in the diagnosis when the condition is suspected.

Obviously it is difficult to diagnose a cyst in the abdomen or pelvis, except when there are calcareous changes in the adventitia. Over 90 per cent of these cysts are secondary, and a history suggestive of rupture of a primary cyst at some time in the past may be obtained. After an injury a patient may give a history of various degrees of anaphylaxis, urticaria or erythema.

31. Dew,[6] p. 106.

Clinically a chessboard arrangement of alternating areas of dulness and resonance may reveal the true condition. This sign is not found in any other condition.

HEART, MUSCLES AND OTHER TISSUES

The heart, muscles and other tissues are rarely involved, and the findings will not be discussed in this paper. However, a roentgenogram made in one interesting case will be included (fig. 8).

LOCALIZATION

After discovering that a cyst is present, the roentgenologist should seek to localize it. This may be done by using films taken with the patient

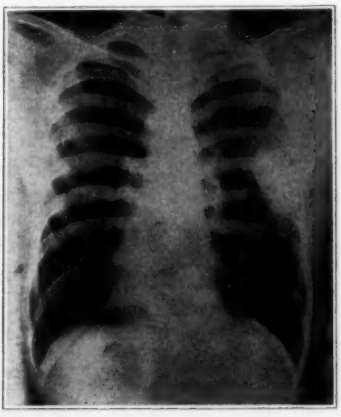


Fig. 8.—A hydatid cyst located in the posterior axillary region and entirely confined to the soft tissue.

in the anteroposterior and in the lateral position or by using stereoscopic films of the chest or abdomen. The best means of localization yet devised is that of Johnson [32] by means of stereoroentgenometry. By this method it is possible to measure accurately the size of the cyst and to determine its position.

Another method recently described involves use of the tomograph, devised by Chaoul,[33] of Berlin. By taking anteroposterior serial roentgenograms through the chest or abdomen in various successive parallel planes it is possible to demonstrate the cyst, its contents and its position accurately.

32. Johnson, Clayton R.: Roentgen Mensuration by Stereoroentgenometry, Radiology **25**:492 (Oct.) 1935.

33. Chaoul, R.: Personal communication to the author.

Pneumoperitoneum.—A few years ago pneumoperitoneum was strongly advocated by Uspensky [34] and others. However, it has failed to be of great diagnostic moment and is not without risk, particularly when infected cysts may be present.

NEEDLING

Promiscuous needling is to be condemned. After this procedure unfortunate sequelae have been recorded, such as introduction of sepsis; contamination of surrounding healthy tissues; puncture of a blood vessel, followed by hemorrhage; rupture of a pulmonary cyst into a bronchus, resulting in anaphylactic shock which sometimes causes death, and death due to drowning.

SURGICAL TREATMENT

Fortunately the anaphylactic state is abolished under general anesthesia, so that serious symptoms are not forthcoming when toxic material is spilled into the wound. However, at times there may be a delayed reaction due to slow absorption of cystic fluid following surgical treatment. Hence it is well for the surgical field to be well protected by packs made of black gauze, so that absorption of hydatid elements can be visualized if spilled and absorption of the fluid avoided.

SUMMARY

The history and distribution of hydatid disease and the life cycle of Taenia echinococcus are considered.

The incidence of hydatid disease of various organs is discussed, and it is shown that the liver is the most frequent site of infection in human beings.

The diagnosis and laboratory tests, including the precipitin, the Casoni and the complement fixation test, are considered.

The roentgenographic findings in the organs and tissues principally involved, together with a brief differential diagnosis, are given.

NOTE.—References cited in footnotes 5, 6, 14, 20, 24 and 25 were included on the authority of other writers.

Dr. Edwards and Professor Harold Dew rendered valuable assistance in the preparation of this article.

34. Uspensky, A. E.: Diagnostic Importance of Pneumoperitoneum, Brit. J. Radiol. **32**:14 (April) 1927.

THE ADRENALS AND EXPERIMENTAL PANCREATIC DIABETES

J. M. ROGOFF, M.D., Sc.D.
AND
H. WARD FERRILL, PH.D.
WITH THE ASSISTANCE OF E. NOLA NIXON
CHICAGO

The etiology and course of diabetes mellitus have been associated with adrenal function by various authors since Zuelzer [1] proposed the view that a mutual antagonism exists between the adrenals and the pancreas. He said he believed that the glycosuria which follows pancreatectomy is due to the unchecked diabetogenic action of epinephrine secreted from the adrenals in the absence of the antagonistic action of internal secretion of the pancreas.

More recently the supposed relationship of the adrenals to diabetes and to other diseases has become the basis for surgical intervention or roentgen irradiation of the adrenals in clinical practice. In view of the fact that these procedures involve possible irreparable damage to the indispensable adrenal cortex as well as to the less essential medulla, they should be based on physiologic premises that have indisputable experimental support, or else they should be condemned as too dangerous for life and health to warrant their use as therapeutic measures. We believe that the experimental background for the alleged relation of the adrenals to diabetes is inadequate. One of us [2] has already emphasized the possible serious consequences of surgical intervention on the adrenal glands and has reported the development of Addison's disease following an operation on a patient with diabetes.

Some writers have maintained that the medulla is concerned with diabetes; others believe that it is the cortex. Some apparently have

---

From the Physiological Laboratory, University of Chicago.

Eli Lilly & Co. supplied the insulin for this and related investigations.

A preliminary report of this work has been published (Proc. Soc. Exper. Biol. & Med. **34**:100, 1936).

Aided by the G. N. Stewart Memorial Fund and grants from the Commodore Beaumont Foundation and Mr. Max Manischewitz.

1. Zuelzer, G.: (*a*) Experimentelle Untersuchungen über den Diabetes, Berl. klin. Wchnschr. **44**:474, 1907; (*b*) Ueber Versuche einer spezifischen Fermenttherapie des Diabetes, Ztschr. f. exper. Path. u. Therap. **5**:307, 1908.

2. Rogoff, J. M.: Addison's Disease Following Adrenal Denervation in a Case of Diabetes Mellitus, J. A. M. A. **106**:279 (Jan. 25) 1936.

considered the adrenal as a single gland, failing to note functional distinction between the indispensable interrenal glandular tissue, or cortex, and the chromaffin material, or medulla, of the adrenal body. An extensive literature has accumulated on the alleged rôle of the adrenals in carbohydrate metabolism, much of which fails to indicate whether the supposed influence of the glands is exercised by the cortex or the medulla or both.

Possible relationship of the adrenal medulla to diabetes can be studied more easily than that of the adrenal cortex. The output of epinephrine can be measured, and the rate of secretion of epinephrine in normal animals under ordinary experimental conditions is known.[3]

Liberation of epinephrine can be suppressed without serious consequences in otherwise normal animals.[4] If secretion of epinephrine plays a significant rôle in experimental pancreatic diabetes, its suppression should affect the development or course of diabetes in depancreatized animals. We have made experimental studies to determine whether this occurs and also quantitative as well as qualitative studies of secretion of epinephrine in relation to experimental pancreatic diabetes.

In previous communications [5] it was reported that unilateral adrenalectomy or interference with secretion of epinephrine (by adrenal denervation and other procedures) ameliorated diabetes in depancreatized dogs, that in animals previously rendered diabetic (by pancreatectomy) the adrenal operation diminished the glycosuria and that in dogs previously subjected to the adrenal operation pancreatectomy failed to cause or caused only a mild degree of glycosuria. The amount of insulin required (on a constant diet) for controlling the glycosuria was reported to be decidedly less as the result of the adrenal operations, which were said also to render the animals more sensitive to insulin. These statements are in agreement with conclusions reported by others.

---

3. Stewart, G. N., and Rogoff, J. M.: The Average Epinephrin Output in Cats and Dogs, Am. J. Physiol. **66**:235, 1923.

4. Stewart, G. N., and Rogoff, J. M.: (*a*) Quantitative Experiments on the Liberation of Epinephrin from the Adrenals After Section of Their Nerves, with Special Reference to the Question Whether Epinephrine Is Indispensable for the Organism, J. Pharmacol. & Exper. Therap. **10**:1, 1917; (*b*) Further Observations Showing that Epinephrine from the Adrenals Is not Indispensable, Am. J. Physiol. **48**:397, 1919.

5. (*a*) Barnes, B. O.; Scott, V. B.; Ferrill, H. Ward, and Rogoff, J. M.: Effects of Partial Adrenalectomy on Experimental Diabetes and on Sensitivity to Insulin, Proc. Soc. Exper. Biol. & Med. **31**:524, 1934; (*b*) The Effects of Partial and Complete Adrenalectomy on Experimental Diabetes, Am. J. Physiol. **109**:35, 1934; Further Studies on the Effects of Partial Adrenalectomy on Experimental Diabetes, ibid. **109**:89, 1934; The Sensitivity to Insulin, ibid. **109**:95, 1934. (*c*) Ferrill, H. Ward; Rogoff, J. M., and Barnes, B. O.: Further Studies on the Influence of the Adrenal Glands on Experimental Diabetes, ibid. **113**:41, 1935.

On further examination of the experimental data and in view of satisfactory control experiments, we found it necessary to revise the foregoing interpretations. Under more suitable conditions, we have repeated the experiments and have made more extensive quantitative studies of the output of epinephrine from the adrenals of experimental animals and of an adequate series of control depancreatized dogs. In the former series of experiments the adrenal operations were performed by one of us (J. M. R., assisted by E. N. N.) and the pancreatectomies by another collaborator (B. O. B., who was assisted by H. W. F.). The postoperative and other experimental conditions were not as satisfactorily controlled as in the present series of experiments. One of the animals (on the history of which was based the statement that little or no diabetes follows pancreatectomy if the adrenals are interfered with) was found at autopsy to possess a substantial portion of pancreas, and in one or two others a number of nodes were observed along the duodenum and were preserved for histologic examination. With improved conditions of experimental procedure and suitable controls, it became obvious that we had been misled in the evaluation of the previous experimental data.

The present report is concerned chiefly with experiments to determine whether reduction or suppression of secretion of epinephrine from the adrenal glands exerts a significant influence on experimental pancreatic diabetes.

In these, as in the earlier experiments, the criterion was the amount of insulin required to maintain the level of sugar excreted in the urine below about 5 Gm. daily and the concentration of sugar in the urine under about 1 per cent. The experiments were performed on dogs. All the experimental and control animals were kept under identical or comparable conditions and on a constant diet, consisting of 500 Gm. of boiled beef lung and 100 Gm. of sucrose daily, divided into two meals. To the morning meal was added 50 Gm. of fresh raw beef pancreas. Drinking water was available at all times. The amount of insulin for each day was divided into two doses and given at the time of feeding. Urine was collected for twenty-four hours; the quantity excreted and the sugar content were determined at the same hour each morning.

Interference with secretion of epinephrine was accomplished by excision of one adrenal gland and denervation of the other gland. In addition to denervation, the medulla of the remaining gland was curetted by drilling with a dental burr so that most of the medulla was destroyed or damaged. For these animals the adrenal operations were performed in two stages, and pancreatectomy was performed during the interval between the adrenal operations. Other dogs were depancreatized without the subjection of the adrenals to operations for reducing the secretion of epinephrine. These served as controls. All the surgical operations in this series were performed by one of us (J. M. R., assisted by E. N. N.). A number of additional experiments were carried out in which the surgical procedures were performed by the other of us (H. W. F.). At the end of different periods of observation the experiments were terminated, so that quantitative determination of the degree of reduction or suppression of secretion of epinephrine could be made (by the method employed by Stewart and Rogoff).

Twenty-one animals were studied in this series of experiments. In these, as well as in some of the better experiments of the previous group, after a few weeks of observation the animals usually showed a reduction in the amount of insulin required to maintain glycosuria at the low level. This cannot be attributed to loss of weight, since the animals of the present series lost little if any weight, although most of the former animals were in much poorer condition. It might appear that in depancreatized animals subjected to interference with secretion of epinephrine from the adrenals the reduced requirement for insulin is due to reduced secretion of epinephrine. However, this cannot be the case, since the requirement for insulin does not decline until several weeks after pancreatic diabetes has been induced. Indeed, it appears at a time when regeneration of nerves might occur in the animals after adrenal denervation and when secretion of epinephrine might be expected to have become reestablished. In any case, the reduction of the amount of insulin required cannot be attributed to the operation for suppression of secretion of epinephrine, since it occurs in control depancreatized dogs not subjected to adrenal operations but otherwise under the same conditions as the experimental animals.

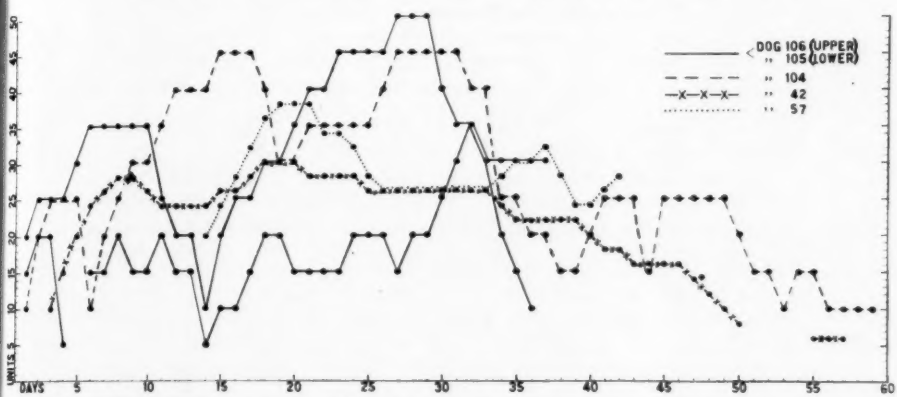
We have observed the decline in requirement for insulin in experimental animals with reduced or suppressed secretion of epinephrine and in some with the ordinary normal rate of secretion (indicating either inadequate denervation or regeneration of adrenal nerves). It is obvious that the requirement for insulin is not modified by the functional state of the adrenal medulla. The range of dosage of insulin required over a period of weeks or months is similar in control depancreatized dogs and in those with a reduced or suppressed output of epinephrine. We have found a high or low requirement for insulin associated with a low or normal output of epinephrine. This may be seen in different animals or in one animal at different times, regardless of whether or not, in addition to pancreatectomy, secretion of epinephrine has been suppressed.

The most significant observation that we have made is that in control depancreatized dogs (not subjected to interference with the adrenals), kept under the same conditions as the other experimental animals, sooner or later the output of epinephrine from the adrenals may become markedly reduced or suppressed. This phenomenon and the possible mechanism responsible for it are still under investigation and will be the subject of another report.

The accompanying chart illustrates the general results obtained. One record (dog 42), the best for the former experiments, is included because the interval between the adrenal operations and pancreatectomy was much longer than that in the later experiments; the rest are for the present series. Each record represents a typical experiment, illus-

trating the various results obtained for different groups of the series. Two dogs (42 and 57) were subjected to operations for suppression of secretion of epinephrine in addition to pancreatectomy; the other three were only depancreatized. These five experiments will be described in the following condensed protocols:

Dog 42.—Both adrenals of this female dog were denervated, and the medulla was drilled, the left on July 13 and the right on July 21, 1934. On Jan. 2, 1935, pancreatectomy was performed. During the ensuing five weeks the requirement for insulin ranged between 24 and 30 units daily; then it declined during the next three weeks to 6 units daily. On March 1 (fifty-eight days after pancreatectomy) the animal (weight, 6.05 Kg.) was killed and the output of epinephrine from the adrenals was determined. With the animal under pentobarbital anesthesia blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 1.53 Gm. per minute. The concentration of



The requirement for insulin, with a daily diet of 500 Gm. of boiled beef lung, 100 Gm. of cane sugar and 50 Gm. of raw beef pancreas, after pancreatectomy with and without suppression of secretion of epinephrine from the adrenal glands of dogs.

epinephrine was estimated, a segment of rabbit intestine being used. The epinephrine concentration in the blood from the adrenal vein was much less than 1: 30,000,000 and somewhat less than 1: 50,000,000, which was the limit of sensitivity for the segment. If the blood from the adrenal vein contained this concentration, it would correspond to 0.00003 mg. per minute for the dog or 0.000005 mg. per kilogram per minute, i. e., about one fiftieth of the average output for normal animals, as determined by Stewart and Rogoff [3] (1923). There probably was not more than one seventy fifth to one one hundredth of the average output of epinephrine for normal dogs under ordinary experimental conditions.

Dog 57.—On April 6, 1935, the right adrenal was removed from this male dog (weight 13.5 Kg.). On April 26 pancreatectomy was performed, the animal weighing 13.7 Kg. On May 9, when the weight was 11.6 Kg., the left adrenal was denervated, and the medulla was drilled. From April 30 to May 3, inclusive, the

dosage of insulin was doubled by mistake (insulin containing 40 units instead of 20 per cubic centimeter being used), reaching 70 or 80 units daily, without ill effect. Thereafter, the requirement for insulin ranged between 24 and 38 units daily. On June 8, forty-three days after pancreatectomy (weight, 11.2 Kg.), the requirement for insulin was 28 units (ascending), and the sugar content of the blood (a. m.) was 320 mg. per hundred cubic centimeters. The animal was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 2.7 Gm. per minute. The remaining adrenal gland (left) weighed 0.57 Gm.; it had undergone fibrosis, and the upper half was sclerotic. The concentration of epinephrine in the blood from the adrenal vein was much less than 1:50,000,000 and not as great as 1:75,000,000. If the blood contained 1:75,000,000 epinephrine, the output would correspond to 0.000035 mg. per minute for the dog, or 0.0000031 mg. per kilogram per minute; i. e., the output of epinephrine was less than one seventy fifth of the average output for normal animals under ordinary experimental conditions.

Dog 104.—Pancreatectomy was performed on this female dog (weight, 8.8 Kg.) on Sept. 26, 1935. The requirement for insulin for about a month ranged between 25 and 40 units daily; then it fell, ranging between 15 and 25 units daily for about three weeks. On November 25 (sixty days after pancreatectomy), when the dog weighed 7.65 Kg., the insulin requirement was 10 units daily. The animal was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 8.67 Gm. per minute. The left adrenal gland weighed 0.64 Gm. and the right gland 0.70 Gm. Epinephrine concentration in the blood from the adrenal vein was distinctly less than 1:125,000,000, somewhat less than 1:250,000,000 and slightly greater than 1:375,000,000. It was taken at 1:300,000,000, corresponding to an output of 0.0000286 mg. per minute for the dog, or 0.0000037 mg. per kilogram per minute, i. e., about one seventieth of the average output of epinephrine for normal dogs under ordinary experimental conditions.

Dog 105.—Pancreatectomy was performed on this male dog (weight, 8.5 Kg.) on Oct. 26, 1935. The requirement for insulin during most of the entire period of observation ranged between 15 and 20 units daily. On Dec. 2 (thirty-seven days after pancreatectomy), when the dog weighed 7.4 Kg. and the requirement for insulin was 10 units, it was used for epinephrine assay. With the animal under pentobarbital anesthesia blood was obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 4.95 Gm. per minute. The left adrenal gland weighed 0.47 Gm. and the right one 0.5 Gm. Epinephrine concentration in the blood of the adrenal vein was greater than 1:12,000,000, somewhat greater than 1:6,250,000 and less than 1:3,750,000. The reaction on the segment of intestine was not unlike that of 1:5,000,000. It was taken at 1:5,000,000, corresponding to an output of epinephrine of 0.001 mg. per minute for the dog, or 0.000135 mg. per kilogram per minute, i. e., within the usual range for normal dogs under ordinary experimental conditions.

Dog 106.—Pancreatectomy was performed on this female dog (weight 9.5 Kg.) on Oct. 26, 1935. The requirement for insulin rose to 50 units daily during about a month and then declined to 30 units daily for the last five days of observation. On December 3 (thirty-eight days after pancreatectomy), when the animal weighed 8.5 Kg. and the requirement for insulin was 30 units daily, it was used for epinephrine assay. With the animal under pentobarbital anesthesia, blood was

obtained from the adrenal vein by way of the "cava pocket." The rate of blood flow during collection was 4.25 Gm. per minute. The adrenal glands weighed 0.56 Gm. each. Epinephrine concentration in the blood from the adrenal vein was decidedly greater than 1:5,000,000, somewhat greater than 1:3,750,000, less than 1:2,500,000 and not far from 1:3,125,000. It was taken at 1:3,000,000, corresponding to an output of epinephrine of 0.0014 mg. per minute for the dog, or 0.00017 mg. per kilogram per minute, i. e., within the usual range for normal dogs under ordinary experimental conditions.

For three animals (dogs 56, 57 and 60) the dose of insulin was doubled by mistake. A supply of insulin containing 40 units per cubic centimeter was used, whereas previously the insulin contained 20 units per cubic centimeter. For four days, instead of the intended 35 to 40 units daily, the animals received 70 to 80 units daily before the error was discovered. In two instances one adrenal gland had been excised and pancreatectomy performed; in the third case one adrenal gland was denervated before pancreatectomy. No ill effects were observed from these enormous doses of insulin. We must conclude, therefore, that in depancreatized animals the supposed increase in sensitivity to insulin reported to occur after unilateral adrenalectomy or adrenal denervation is without foundation. A number of animals that had only been depancreatized were killed at intervals of about one to eight weeks after removal of the pancreas. The output of epinephrine was determined for these to observe how soon reduction might be detected. In some the requirement for insulin at the time was relatively high; in others it was low. A reduction in the secretion of epinephrine was found as early as ten and eleven days after pancreatectomy in some animals, while in others a normal output of epinephrine was found five or six weeks after pancreatectomy. We found no relation between the requirement for insulin and the rate of secretion of epinephrine in the animals studied.

COMMENT

The literature on the adrenal glands in relation to carbohydrate metabolism is too extensive for us to attempt more than a review of a few papers that have a more or less direct bearing on the particular phase of the subject under consideration. The earlier papers are concerned chiefly with the question of relationship of the adrenal medulla, although some of them do not make clear whether a relationship of the medulla or of the cortex is supposed to exist. In the more recent literature can be found support for either view, i. e., that the cortex plays an important or indispensable rôle in carbohydrate metabolism or that the medulla plays such a rôle.

Studies of the influence of administration of epinephrine on carbohydrate metabolism may be viewed as being mainly of pharmacologic interest. Few investigations of this nature can have physiologic sig-

nificance, since the dosage of epinephrine is usually much in excess of the amounts known to be within the physiologic range of secretion. Often the epinephrine is administered subcutaneously. Owing to the local vasoconstrictor action of epinephrine absorption is rarely at a uniform rate, indeed, differences in physiologic action have been reported between the subcutaneous and the intravenous administration of the same quantities of epinephrine.

Of those who have supported the view that the cortex is directly concerned in an important manner with carbohydrate metabolism, none can be said to have produced adequate experimental proof. Britton and Silvette [6] have maintained that the adrenal cortex exercises a "prepotent function" on carbohydrate metabolism and that in adrenalectomized animals the effect on carbohydrate metabolism "appears to be primarily responsible for death." Rogoff and Stewart [7] have shown that moderate hypoglycemia occurs in adrenalectomized animals when acute symptoms of cortical insufficiency develop. However, some animals may manifest important symptoms of insufficiency and show no significant decline in the sugar content of the blood. This is true, also, for human beings with Addison's disease. The view held by Britton and Silvette that severe hypoglycemia, "commonly to the convulsive level," occurring in animals "as early as 18 to 48 hours after operation," accounts for death of adrenalectomized animals is not tenable in the light of the experimental work of others. The results indicated that their adrenalectomized animals were not in as good condition as they should have been from eighteen to forty-eight hours after operation.

Hartman and Brownell [8] reported studies on nine cats and concluded that their results indicated that "cortin is essential for the maintenance of diabetes." Although they administered an extract of adrenal cortex, most of their adrenalectomized animals did not survive as long as untreated adrenalectomized cats usually do.[9] Of course these were also depancreatized. Nevertheless, the conclusions need not be accepted merely because this additional handicap existed. The experiments would be of value only if the depancreatized and adrenalectomized animals

6. Britton, S. W., and Silvette, H.: The Apparent Prepotent Function of the Adrenal Glands, Am. J. Physiol. **100**:701, 1932.

7. Rogoff, J. M., and Stewart, G. N.: Studies on Adrenal Insufficiency in Dogs: II. Blood Studies in Control Animals Not Subjected to Any Treatment, Am. J. Physiol. **78**:711, 1926.

8. Hartman, F. A., and Brownell, K. A.: Relation of Adrenals to Diabetes, Proc. Soc. Exper. Biol. & Med. **31**:834, 1934.

9. Rogoff, J. M., and Stewart, G. N.: (*a*) Studies on Adrenal Insufficiency: VIII. The Survival Period of Untreated Adrenalectomized Cats, Am. J. Physiol. **88**:162, 1929; (*b*) Studies on Adrenal Insufficiency: IX. The Influence of Extracts of Adrenal Cortex (Sheep and Cattle) on the Survival Period of Adrenalectomized Dogs and Cats, ibid. **91**:254, 1929.

were in sufficiently good condition to permit studies that were not complicated by serious postoperative conditions. Indeed, the only cat that survived long enough to permit satisfactory studies showed a condition exactly opposite to that mentioned in their conclusion. The animal survived thirty-eight days after bilateral adrenalectomy. "For three weeks or more during this latter period there was no reduction in diabetes but after this time there was marked reduction which large amounts of cortin failed to restore." Adrenal cortex extract prepared by Hartman's salt precipitation method has been proved to be incapable of prolonging life in adrenalectomized animals.[9b] Since then he has employed extracts of adrenal cortex prepared by a different process. It may be pointed out that since Hartman [10] has maintained that the adrenal cortex produces epinephrine, he could not be certain that any effect attributed to action of his extract might not have been due to presence of epinephrine or related principles.

From the pharmacologic antagonism existing between epinephrine and insulin it seems that the alleged relation of the adrenal medulla to pancreatic diabetes rests on a more substantial basis. However, the evidence afforded by properly controlled experimental work and by adequate quantitative studies does not show such a relationship. Older literature on this question has been reviewed in a number of papers by Stewart and Rogoff [11] on carbohydrate metabolism, particularly in the paper entitled "The Adrenals and Pancreatic Diabetes." [12] In that paper it was shown that diabetes develops in depancreatized animals in the absence of secretion of epinephrine to the same degree as in those without interference with the adrenals. After total ablation of the adrenals pancreatic diabetes continues to exist if the postoperative consequences of adrenalectomy are not too severe. If adrenalectomy is followed by a rapid decline of the animal and short survival or if after a period of good postoperative recovery acute insufficiency of adrenal cortex supervenes, the sugar content of the blood may fall to or below the normal level, and glycosuria may become considerably diminished.

10. Hartman, F. A., and Hartman, W. B.: The Production of Epinephrin by the Adrenal Cortex, Am. J. Physiol. **65**:623, 1923.

11. Stewart, G. N., and Rogoff, J. M.: The Alleged Relation of the Epinephrin Secretion of the Adrenals to Certain Experimental Hyperglycemias, Am. J. Physiol. **44**:543, 1917; The Relation of the Adrenals to Piqûre Hyperglycemia and to the Glycogen Content of the Liver, ibid. **46**:90, 1918; Further Observations on the Relation of the Adrenals to Certain Experimental Hyperglycemias (Ether and Asphyxia), ibid. **51**:366, 1920; The Action of Insulin on Adrenalectomized Rabbits, ibid. **65**:342, 1923.

12. Stewart, G. N., and Rogoff, J. M.: The Adrenals and Pancreatic Diabetes, Am. J. Physiol. **65**:319, 1923.

Turcatti [13] concluded that combined pancreatectomy and adrenalectomy interfere with the development or reduce the severity of pancreatic diabetes. This did not occur if, instead of adrenalectomy, the glands were denervated. He admitted that his conclusions cannot be considered categorical, since the animals survived for too short a time. None of his fourteen experimental animals survived beyond forty hours. All succumbed within from eight to forty hours.

Carrasco Formiguera and Puche [14] concluded that denervation of the adrenals does not influence pancreatic diabetes. Their experiments were made on two dogs, in one complete and in the other partial pancreatectomy having been performed. Ciminata [15] has supported the view that diabetes in human beings can be successfully treated by denervation of the adrenal glands. This is based on his experiment performed in 1928 on one dog in which he obtained a rapid decrease in the sugar content of the blood and in glycosuria after bilateral denervation of the adrenals.

Cannon, McIver and Bliss [16] obtained an increase in rate of the denervated heart after administration of insulin, when the sugar content of the blood fell to between 70 and 80 mg. per hundred cubic centimeters in cats anesthetized with a compound of chloral and dextrose. This increase in heart rate was interpreted as indicating liberation of epinephrine from the adrenals to counteract the insulin hypoglycemia. The effect was not obtained if the adrenals were excised or denervated. It is now evident that the "denervated" heart is not a reliable indicator for quantitative studies on the secretion of epinephrine from the adrenals. Cannon, Lewis and Britton [17] have shown that the so-called denervated heart (as employed by Cannon, McIver and Bliss) may not be entirely denervated, since they found "evidence for accessory accelerator fibers from the thoracic sympathetic chain." Other evidence from the same laboratory shows that the cardio-acceleration may be obtained by influence of the thyroid and of the liver, as well as of the

13. Turcatti, E.: Surrénale et diabète pancreatique, Compt. rend. Soc. de biol. **102**:466 (Nov. 8) 1929.

14. Carrasco Formiguera, R., and Puche, J.: Enervation des surrénales et diabète expérimental, Compt. rend. Soc. de biol. **108**:171 (Oct. 12) 1931.

15. Ciminata, A.: Influence of Division of Nerves of Suprarenals on Diabetes Mellitus, Klin. Wchnschr. **11**:150 (Jan. 23) 1932; abstr., J. A. M. A. **98**:1421 (April 16) 1932.

16. Cannon, W. B.; McIver, M. A., and Bliss, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XIII. Sympathetic and Adrenal Mechanism for Mobilizing Sugar in Hypoglycemia, Am. J. Physiol. **69**:46, 1924.

17. Cannon, W. B.; Lewis, J. T., and Britton, S. W.: Studies on the Conditions of Activity in Endocrine Glands: XVII. A Lasting Preparation of the Denervated Heart for Detecting Internal Secretion, with Evidence for Accessory Accelerator Fibers from the Thoracic Sympathetic Chain, Am. J. Physiol. **77**:326, 1926.

adrenal. Finally, the acceleration can be obtained even in the absence of the adrenals or of the influence of the thyroid or liver. It has been accounted for by Cannon and his collaborators as due to a sympathomimetic hormone, which they called sympathin. The reaction relied on by Cannon, McIver and Bliss therefore could not yield reliable quantitative information on adrenal secretion of epinephrine.

Whether or not insulin is capable of influencing secretion of epinephrine has not been satisfactorily determined. Statements can be found in the literature indicating that insulin is without effect and others that it may affect secretion of epinephrine in either direction. Methods of investigation on which these statements are based are not sufficiently reliable. In our own experience, by collecting blood from the adrenal vein by way of the "cava pocket" and utilizing rabbit intestine for determining the concentration of epinephrine in the blood, we have failed thus far to find any significant alteration in the rate of secretion of epinephrine from the adrenals after administration of insulin under the conditions of our experiments. This question is still under investigation.

We believe that the experiments reported in this paper are adequate to show that the alleged relation between the adrenal medulla and pancreatic diabetes does not exist. As in the experiments of others, when we made observations on animals that were in poor condition, we also found milder diabetes. This we interpret as indicating that the condition of the animal was too poor to enable it to react by the development of glycosuria of the same intensity as may occur in depancreatized animals in good condition. For the animals that withstood the experimental conditions better and were obviously in a much more satisfactory physical state, our experiments clearly showed that pancreatic diabetes is not modified by a reducing or suppressing of secretion of epinephrine from the adrenals. On the other hand, we have obtained evidence that the diabetic state, under the conditions of our experiments, may lead to interference with liberation of epinephrine from the adrenals. We believe, therefore, that the supposed relation of the adrenal medulla to diabetes as a basis for the clinical practice of intervention with the adrenal glands does not have the support of unequivocal experimental evidence.

CONCLUSIONS

The supposed dependence of experimental pancreatic diabetes on secretion of epinephrine from the adrenals is not supported by substantial experimental evidence.

Severity of diabetes in depancreatized dogs is not modified by reduction or suppression of secretion of epinephrine from the adrenals.

The requirement for insulin, when the diet is constant, is within the same range in depancreatized dogs as in dogs with a reduced or suppressed secretion of epinephrine in addition to pancreatectomy.

Depancreatized dogs with a reduced or suppressed secretion of epinephrine are not more sensitive to insulin than ordinary depancreatized dogs.

Depancreatized dogs kept for several weeks on a constant diet with adequate amounts of insulin to control glycosuria sooner or later show a reduction or suppression of output of epinephrine from the adrenals.

Results obtained for depancreatized animals that have been subjected to operations on the adrenals should be interpreted with caution unless the animals are obviously in excellent physical condition.

The clinical practice of intervention with the adrenal glands for the relief of diabetes (or other conditions, except unilateral malignant neoplasm) does not rest on unequivocal experimental premises, and it should be deprecated as too dangerous for life and health.

WEIL'S DISEASE

REPORT OF SEVEN CASES

ARTHUR R. GAINES, M.D.
Major, Medical Corps, United States Army
AND
RICHARD P. JOHNSON, M.D.
Captain, Medical Corps, United States Army

Weil's disease has been recognized since Weil described the condition in 1886. Whether or not Weil's four cases were actually cases of spirochetal jaundice is not known, since laboratory confirmation was not possible then. Japanese investigators [1] in 1916 published the results of their study of the disease in their country and established the identity of the causative organism, later named Leptospira icterohaemorrhagiae.[2] Since 1916 cases have been reported from Europe, Asia, Africa, South America and North America and Australia.[3] In the United States and Canada thirteen cases have been reported in which the etiologic agent was shown to be L. icterohaemorrhagiae.[4] In these thirteen cases the clinical course did not differ materially from the usual course.[5] In five cases the diagnosis was not made until autopsy.[6]

Some confusion exists in the diagnosis of Weil's disease, consisting chiefly in the differentiation of the disease from infectious jaundice. Weil's disease is a type of infectious jaundice, but all cases of infectious jaundice are by no means to be considered as cases of Weil's disease. Numerous epidemics of infectious jaundice have been investigated in this country, but in no instance were the investigators able to prove the presence of Weil's disease as a part of the epidemic.[7] Blumer, in 1923, stated that spirochetes had not been demonstrated in any case of jaundice in the United States. The only case reported in the American literature prior to the publication of Blumer's article was that of an accidentally infected laboratory worker.[8] Langworthy and Moore have stressed the

---

From the Medical Service of Fitzsimons General Hospital, Denver.

1. Inada, Ido, Hoki, Kaneko and Ito.
2. Noguchi, 1918.
3. Wadsworth and others; Hübner and Reiter, and Uhlenhuth and Fromme, 1915.
4. Wadsworth and others; Ball, and Jeghers, Houghton and Foley.
5. Inada.
6. McDowell; Bates; Ball, and Jeghers, Houghton and Foley.
7. Wadsworth and others and Blumer.
8. Wadsworth and others.

fact that jaundice is only a symptom occurring in the course of many infectious diseases and that when the exact nature of the infectious disease is not known the condition is simply called infectious jaundice. Epidemic infectious jaundice may well be a definite entity the exact cause of which has not been found, despite many thorough investigations.

Weil's disease is an entity with a definitely known cause. The source of infection, rat infestation with L. icterohaemorrhagiae pathogenic for guinea-pigs, is known to be generally distributed over the entire United States.[9] The organisms described in this country are considered identical with those in Europe and Japan. Leptospira represents a type of spirochete and differs from Spirochaeta pallida in that the spirals are more numerous and more tightly coiled. The most characteristic morphologic feature of L. icterohaemorrhagiae is its sharp, tapering, hooked ends, which are set at an angle to the main axis, giving the whole organism a resemblance to the letter C or S. The organism has been fully described and successfully cultivated by Noguchi.[2]

Norwegian and black rats and mice constitute the essential source of Leptospira. Probably through contamination with the urine of these animals water and slime have also been found to harbor the organism. The rat is a carrier and is not subject to the disease. Not all strains of Leptospira are pathogenic, particularly those found in water or slime, but the virulence can usually be raised by passage through a guinea-pig or a human being, so that the organism becomes pathogenic.[10] Pathogenic leptospiras may remain alive for months in a suitable natural environment, such as wet ground soil from a mine or in pit water.[11] Adequate drainage and changing the soil reaction to mildly acid have been found to eradicate the organism.[12] This point was noted on the western front during the World War, as the soldiers in adequately drained trenches and bases were free from spirochetal jaundice.[13] In 1914 Wolbach and Binger found spirochetes morphologically similar to L. icterohaemorrhagiae in stagnant natural water. Since then this organism has been found in natural water throughout the world and is known as Leptospira biflexa; it is nonpathogenic. Pathogenic strains, other than L. icterohaemorrhagiae, known at present include Leptospira hebdomadis, the cause of Japanese seven day fever; Leptospira grippotyphosa, the cause of the swamp fever of eastern Europe, and Leptospira canicola, which produces in dogs a disease similar to Weil's disease.

9. Wadsworth and others; Noguchi, 1917; Jobling and Eggstein; Neill, and Otteraaen.

10. Baermann and Zuelzer.

11. Buchanan.

12. Inada and others, 1916; and Ido, Hoki, Ito and Wani.

13. Stokes, Ryle and Tytler.

The mode of transmission of this disease from infected rats or water to man is not definitely known. The disease has been reported as occurring after a rat bite,[14] handling a culture of the organism and becoming infected through a needle prick of the skin [8] and after falling into a ditch of liquid manure and swallowing some of the material.[15] Direct contact was considered responsible for the spread of the disease in cases occurring among children.[16] Uhlenhuth and Zuelzer have stated that oral infection in man is exceedingly unlikely because the leptospiras are rapidly killed by the acid of the gastric juice and by the bile of the intestine. Japanese investigators [14] have reported the production of the disease in guinea-pigs by the oral administration of the organism and also by the application of the infectious material on abraded and on unabraded skin. Experimentally this disease has been transmitted to the guinea-pig by the house-fly,[17] stable-fly,[18] bedbugs [19] and possibly by Aedes Aegypti.[20] Among the types of workers frequently mentioned in connection with this disease are sewer workers, butchers, mine workers, fish cutters, rice-field workers, workers in breweries and slaughter houses, bargemen and soldiers (World War).

Inada divided the disease into three stages, namely, a first, or febrile, stage, a second, or icteric, stage and a third, or convalescent, stage. The first, or febrile, stage is characterized by the usual symptoms of an acute infectious disease. It continues from the onset to about the seventh day. The main symptoms, initiated with chills and high fever, are intestinal disturbances, headache, cramping muscular pains, marked hyperemia of the conjunctivae and albuminuria. Death rarely occurs during this stage. Dark field examination of the blood demonstrates the presence of leptospiras. The organisms are also excreted in the urine in this stage, and the injection of urine into guinea-pigs results in a typical reaction. From the fourth day on there is gradual disappearance of the organisms from the blood stream. This is due perhaps to the action of antibodies in the blood. The second, or icteric, stage continues for about one week. As a rule there is a gradual subsidence of the symptoms of the first stage, and jaundice, hemorrhagic diathesis, marked general weakness, nervous symptoms and cardiac weakness develop. Most deaths occur during the second stage. The third, or convalescent, stage begins about the end of the second week. The

14. Ido, Hoki, Ito and Wani.

15. Schürer and Stirl.

16. Lyon and Buchanan.

17. Reiter.

18. Uhlenhuth and Kuhn.

19. Blanchard, Lefrou and Laigret.

20. Noguchi, 1919; Gay and Sellards; Schüffner and Mochtar, and Aitken, Connal, Gray and Smith.

jaundice subsides, and anemia and marked emaciation become prominent. Leptospiras completely disappear from the blood, owing to the further development of antibodies. Increasing numbers of organisms are excreted in the urine, so that by the nineteenth or twentieth day dark field examination of the urine usually reveals their presence. From the twenty-fifth day the number of patients showing organisms in the urine decreases. By the fortieth day practically all patients are free from the organisms. There frequently occurs during the third stage a recurrence of fever. The fever is markedly remittent, and Inada said he prefers to call it an after-fever rather than a relapsing fever, for the

TABLE 1.—*Signs and Symptoms in the Twenty Cases of Weil's Disease Reported in the United States and Canada*

	Previously Reported Cases													Our Cases						
Signs and Symptoms	1	2	3	4	5	6	7	8	9	10	11	12	13	1 14	2 15	3 16	4 17	5 18	6 19	7 20
Initial chill	0	?	+	?	+	+	+	+	+	0	?	+	+	0	0	0	0	0	0	0
Fever	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	0	0	0	+	0
Jaundice	0	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Intestinal disturbances	+	+	?	?	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Nervous symptoms	?	+	?	+	+	+	+	+	+	+	+	?	+	+	0	+	+	+	+	+
Muscular pains	?	+	+	+	+	+	+	?	+	?	?	+	0	+	0	+	+	0	0	
Conjunctival congestion	?	?	0	0	+	0	?	?	0	0	?	?	+	0	+	0	0	0	0	0
Hemorrhagic diathesis	?	+	?	+	+	+	+	+	?	0	?	+	+	+	+	0	0	+	+	+
Enlargement of the liver	?	?	0	+	+	+	+	+	+	+	+	0	+	0	+	0	+	0	0	0
Palpable spleen	?	?	0	0	0	0	0	+	0	0	0	0	0	0	0	0	+	0	0	0
Leukocytosis	+	?	?	0	+	+	+	+	+	+	+	0	+	0	0	0	+	0	0	0
Achylia	?	?	?	?	?	?	?	?	?	?	?	?	?	?	+	0	0	?	0	?
Leptospiras in blood	+	0	+	?	?	+	0	?	?	0	?	?	?	+	+	+	+	+	+	+
Leptospiras in urine	?	0	?	?	?	?	0	?	?	0	?	?	?	0	0	0	0	0	0	0
Leptospira in sections at autopsy	?	+	?	?	+	?	?	?	?	?	+	+	+	?	0	?	?	0	?	?
Positive result of guinea-pig test	+[2]	0	?	+[1]	?	+[2]	+[2]	+[1]	+[1,3]	+[2]	+[4]	0[4]	?	+[1]	+[1]	+[2]	+[2]	?	?	?
Direct van den Bergh reaction	?	?	?	+	+	?	+	?	?	+	+	0	?	+	+	+	+	0	+	+
Outcome	R	D	R	R	D	D	R	R	R	R	D	D	D	R	D	R	R	D	R	R

In this table 0 indicates absence of the symptom or sign; +, its presence; ?, no mention or the test was not done; D, death; R, recovery; 1, using the urine of the patient; 2, using the blood of the patient; 3, using the cerebrospinal fluid of the patient; 4, using macerated renal tissue from the patient.

reason that none of the signs or symptoms essential to a diagnosis of the original disease is present. The cause of the recurrence is still in doubt. The symptomatology for all the cases reported in the North American literature, including the present series, appears in table 1 and figure 1.

Dawson, Hume and Bedson have studied the pathologic picture of this disease. They found that the principal pathologic changes are confined to the abdomen, especially the duodenum, the liver and the kidneys. The duodenum has shown a definite inflammatory reaction, most marked about the ampulla of Vater. The bile ducts are generally normal, except in the last ½ inch (1.5 cm.) of the common duct lying within the duodenal wall. This is found to be swollen, resembling the inflammatory condition in the duodenum. In one patient a plug was

found obstructing the outlet of the common duct. This is mentioned especially because of the pathologic picture presented by our second patient.

The liver is usually normal on gross examination, except that it is bile stained. Microscopically the pathologic picture varies greatly. Occasionally the organ is normal. Again there may be seen both hypertrophy and hyperplasia. Bates observed both minute and large areas of necrosis. There may be a small amount of leukocytic infiltration.

The kidney is usually swollen, and the capsule is tensely stretched. The cells of the tubules are swollen and degenerated or necrotic. The

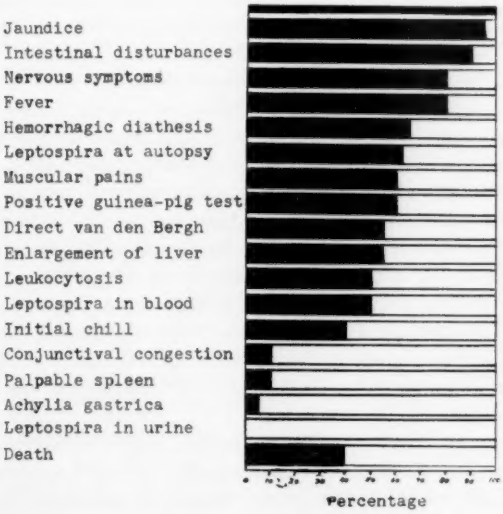


Fig. 1.—The frequency of various signs and symptoms as noted in twenty cases of Weil's disease. The black column indicates the percentage of patients showing the symptom.

glomeruli are congested, and their cells are degenerated. There are scattered collections of polymorphonuclear leukocytes in and between the tubules. Hemorrhages occur into the lumen of the tubules.

No other organs are typically affected. The lungs may occasionally show hemorrhagic areas, but this has been noted less frequently in human beings than in inoculated guinea-pigs. Bates reported that the skeletal muscles, particularly those of the calf, present evidence of hyaline degeneration and necrosis of the fibers, with surrounding inflammatory infiltration. The pathologic picture, in brief, is that of jaundice, hemorrhages due to capillary damage and the congestion and

necrosis of the liver and kidneys as it occurs in any acute infection. The appearance is not so distinctive as to permit a pathologic diagnosis without the aid of other studies.

The guinea-pig, about six days after intraperitoneal inoculation with infected blood or urine, has a fever and becomes toxic and then jaundiced. It usually dies the tenth day or later, depending on the presence of immune bodies in the blood. At necropsy, besides recovery of the organism from the blood, urine, liver and kidney, the following pathologic picture is usually noted: generalized icterus, petechiae, hemorrhages in the lungs, acute congestion of the kidneys, with minute hemorrhages and large hemorrhages in the adrenal glands.

Weil's disease is usually given consideration only in cases of acute febrile jaundice. In view of our experience we believe that this disease should be considered in every case of unexplained jaundice. The diagnosis cannot be made on clinical evidence alone and must be confirmed by at least one of the following methods: first, dark field examination or smear of blood showing L. icterohaemorrhagiae; second, the demonstration of L. icterohaemorrhagiae in the urine; third, injection of blood or urine into the guinea-pig, with subsequent production of typical lesions and recovery of the organism, and fourth, the demonstration of specific antibodies in the blood either by means of the Pfeiffer reaction or by direct agglutination with a known strain.[21] This last reaction has been obtained twelve years [22] and even twenty-two years [23] after the original illness. Less important methods of diagnosis, as mentioned by Jeghers and his associates, include culture of the patient's blood,[24] complement fixation test (Gaehtgens),[25] the precipitation test [26] and the adhesion test.[27]

In our experience examination of the blood by direct dark field examination was the most satisfactory method of diagnosis and gave positive results for all our patients. Some had as high as 25 organisms per high power field, and in none was the search time-consuming, for practically every field contained a few of the organisms. The urine was examined, but leptospiras were not found by this method. An exhaustive search was not made in any case because organisms were demonstrated in the blood. In four of our seven cases the diagnosis was confirmed not only by examination of the blood but by guinea-pig inoculation with blood in two cases and with urine in two other cases.

21. Schüffner.
22. Fairley.
23. Uhlenhuth and Fromme, 1930.
24. Manteufel.
25. Gaehtgens.
26. Hindle and White, and Lusena and Carlinfanti.
27. Brown.

with positive findings. It is to be noted that our second and seventh patients possibly had had the disease for eight months before the diagnosis was made and confirmed; also that for our third and fourth patients leptospiras were easily demonstrable in the blood for nine and five weeks, respectively.

The disease is so little known in this country and the clinical picture so variable that to mention a list of diseases which it may resemble is useless. Weil's disease must often be suspected on minimal grounds, and the suspicion must be confirmed or rejected by laboratory examination. In the patients reported on in North America jaundice was present and furnished the basis for the laboratory examination in all except the first case.[8] However, as pointed out by Jeghers, this symptom is often not mentioned in case reports from Europe and Japan and therefore cannot form the only basis for suspecting the presence of the disease. Any of the listed symptoms, especially cramping muscular pains, hemorrhagic diathesis and enlargement of the liver, in the absence of other adequate explanation, may be important leads.

The prophylactic treatment with immune horse serum in countries where the disease is endemic has been successfully used. In the treatment of patients with active involvement convalescent serum and immunized horse or goat serum are equally effective. The mortality rate from this disease in Japan has been materially reduced by the use of immune horse serum.[28] Rabbit serum has been used by Uhlenhuth and Fromme [23] in epidemics because they found it possible to produce antibodies in the blood of the rabbit more quickly than in that of the horse or goat. Polyvalent serum is preferable because of the heterogeneity of the organism.[29]

Convalescent whole blood from our third patient was used in the treatment of our fourth patient. The initial injection resulted in a diminution in the number of organisms, but a second injection was necessary before the organisms disappeared entirely from the blood. Convalescent serum was used for our fifth, sixth and seventh patients, with prompt disappearance of the organisms from the blood.

Arsphenamine and other arsenicals are said to be worthless as aids in the treatment, according to standard textbooks and articles. Inada and his co-workers [1] have shown that the leptospiras are removed from the blood of the guinea-pig by arsphenamine though not as effectively as with convalescent serum or immunized goat or horse serum. One of the principal objections to the use of an arsenical is that it may increase the hepatic damage. Our third patient was shown to have leptospiras in the blood after sixty days, though during the previous thirty days the liver had shown no damage either clinically or by laboratory tests.

28. Inada, Ido, Hoki, Ito and Wani.
29. Baermann and Smits.

Neoarsphenamine (0.3 Gm.) was given intravenously at this stage, and leptospiras were not again demonstrable in the blood or urine. This prompt result could hardly have been coincidental.

REPORT OF CASES

CASE 1.—M. A., a printer aged 32, was admitted to the hospital on Jan. 7, 1932. The chief item of interest in the history was that he had worked and lived in many places. At the onset of the illness he was living in a cheap hotel, which he stated was rat infested. On January 1 he had cramplike pains in the upper portion of the abdomen, with moderate nausea and vomiting. The following day he felt improved, but a day later there was a recurrence of the original symptoms, accompanied with diarrhea. The patient next noted that the urine was "strong and burned" and that there was considerable frequency. He was restless and did not sleep well. Pyrosis became marked. On January 6 he first noted that his skin was yellow. Moderate cough, fever and headache developed at this time. Blood-tinged expectoration occurred the day prior to his admission to the hospital.

Examination.—The patient was acutely ill, with a temperature of 103.4 F. The skin and mucous membranes were markedly icteric. The blood pressure was 112 systolic and 60 diastolic. There was noted considerable tenderness over the liver and gallbladder. The blood was examined by the dark field method the day following the patient's admission to the hospital, and many leptospiras were observed in each high power field. Two guinea-pigs were inoculated intraperitoneally with the patient's urine on January 8. The pigs died on January 23 and 24, respectively. They had been acutely ill and had showed jaundice; leptospiras were recovered. Dark field examination of the patient's urine did not reveal leptospiras. The icterus index on January 8 was 80, and on January 24 it was 45. The van den Bergh test showed a prompt direct reaction. The Wassermann and Kahn reactions of the blood were negative. The white blood cell count was 7,900, with 64 per cent polymorphonuclears. The red blood cell count was normal. Repeated urinalysis revealed no abnormality except for the presence of bile.

Course.—The temperature ranged from 99.8 to 103.4 F. for three days after the patient's admission to the hospital, and thereafter it was normal except for an occasional reading of 99 F. The pulse rate was always under 100 and usually under 90. The blood no longer showed leptospiras after about the tenth day of illness, and the urine gave a negative response to guinea-pig inoculation after the twenty-first day. The jaundice and the tenderness in the right upper quadrant of the abdomen subsided more slowly, but recovery was complete. Treatment was symptomatic.

CASE 2.—E. V. M., a Negro automobile mechanic aged 37, was admitted on Jan. 19, 1935. He had lived in Denver for the past two years and had been in good health until May 1934, eight months prior to admission to the hospital. At that time he commenced to feel sluggish, had no energy and became nauseated and vomited soon after eating. A few days later he noticed that the stools were light clay colored, and they remained so. The urine became dark and the eyeballs were yellow. Coincident with the appearance of jaundice the patient had a feeling of discomfort in the right upper quadrant of the abdomen. The pain was dull. There was no sharp or colicky pain at any time. The jaundice increased steadily until August and then remained about the same. Itching of the skin had been present since July. Throughout this illness the patient worked steadily at his usual

occupation until two weeks prior to his admission to the hospital. At various periods during the eight months there was aching of the muscles, particularly in the calves of the legs. There was a total loss of 37 pounds (16.8 Kg.). Constipation, not present originally, became a prominent symptom during the month preceding his admission to the hospital. The appetite remained good, but the patient refrained from eating because of postprandial gaseous distention.

Examination.—The patient was ambulatory, afebrile, well developed and well nourished, with prominence of the upper portion of the abdomen. He did not appear acutely ill. His weight was 133 pounds (60.5 Kg.), and his height was 5 feet 4½ inches (164 cm.). There was marked icterus of the skin and mucous membranes. The conjunctivae were injected. The special senses were grossly normal. Mild oral sepsis due to periodontoclasia was present. There was slight generalized lymphadenopathy. The thyroid gland was normal. The tonsils were buried. The pulse beats were equal, soft and regular, with a rate of 76. The heart was normal in size and position; no thrills, shocks or murmurs were noted, and the tones were normal. The blood pressure was 116 systolic and 82 diastolic. The lungs were resonant throughout, and the breath sounds were normal. The

TABLE 2.—*Chemical Study of the Blood of the Second Patient*

Date	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea Nitrogen, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Serum Bilirubin, Mg. per 100 Cc.	Icterus Index	Rosenthal Test	Sugar, Mg. per 100 Cc.
1/22	32.6	....	.....	....	75	....	77
1/24	38.0	16.5	210.0	....	94	....	..
1/29	....	....	.....	....	120	....	..
1/31	28.0	14.5	196.0	....	85	....	..
2/ 7	24.0	10.0	320.0	19.4	56	....	..
2/15	28.0	11.5	418.0	....	100	....	..
2/21	19.0	12.9	532.8	....	100	20% retention in 30 min.	..
2/28	....	....	.....	42.8	...	....	..
3/ 3	....	....	.....	45.7	...	....	..

entire genito-urinary system appeared normal. The abdomen was rounded, with prominence of the right upper quadrant. The liver was enlarged to 3 finger-breatdhs below the costal margin and was tender, particularly over the gallbladder, which appeared as a bulging mass the size of an orange, moving with respiration but not distinctly palpable. The spleen was not palpable. There were no other masses in the abdomen. The pupils were slightly irregular but reacted to light and in accommodation. The superficial and deep reflexes were normal. There was no Babinski or Romberg sign or any sensory disturbance. The cranial nerves were normal. The skeletal system was grossly normal. The muscles of the calves were tender to pressure.

Laboratory and Special Examinations.—The results of the chemical studies of the blood are given in table 2. The van den Bergh test gave a prompt direct reaction. The clotting time was three minutes, but it fluctuated between two and five minutes until February 21, when it was eighteen minutes. On March 5, the day prior to operation, the clotting time was seven and one-half minutes. On January 21 the blood was examined by the dark field method and found to be teeming with leptospiras. That day a guinea-pig was inoculated intraperitoneally with the patient's blood. On January 29 the pig died, and autopsy showed icterus and generalized hemorrhages. Leptospiras were easily recovered. The blood was examined for organisms on three other occasions, but none was found. The urine

showed no organisms by dark field examination, and except for moderate albuminuria and a bile-stained color, it was normal. The urinary output was increased, on one occasion being 4,000 cc. in twenty-four hours. The stools showed no ova or parasites, but occult blood was present. The red blood cell count prior to operation varied from 4,200,000 to 3,300,000. After operation the count fell and was 2,200,000 the day preceding death. The white blood cell count was low, varying from 3,700 to 6,500 before operation. Thereafter there was a sharp rise to 13,000 and later to 17,000, on the day of death. The differential count showed constant eosinophilia, with 3 per cent or more and on one occasion 8 per cent eosinophils. The blood platelet count was 285,000. Gastric analysis by the fractional method showed achylia, with the highest total acidity 16. The Wassermann and Kahn reactions of the blood were negative.

Course.—The original impression in this case was of obstructive jaundice. There was continuation of the clay-colored stools and the dark-colored urine. Because of the presence of unexplained jaundice and muscular cramps, dark field examination of the blood was carried out, and leptospiras were demonstrated. Rechecking of the history at this time in reference to contact with rats revealed that the patient had never to his knowledge been bitten by a rat, but that both his home and his place of work were rat infested. On January 25 a duodenal tube was passed, but no bile was obtained. On January 26 some yellow alkaline fluid was obtained, but on repeated drainage thereafter no trace of bile was obtained. Twenty-four hours after the patient's admission to the hospital fever developed and was intermittent from that time on, the temperature ranging from 96.4 to 102.8 F. The pulse rate ranged from 72 to 108. Symptomatic treatment included a low fat-high carbohydrate diet, duodenal drainage, with daily instillation of magnesium sulfate, hot moist compresses over the liver, alkaline water and methenamine. On February 6 a note was made that nosebleeds had been occurring for several days. Up to February 14 the patient's condition was essentially stationary, except that the liver was less tender, the urine was lighter and pruritis varied from minimal to marked. From this time on, however, the course was downward. The patient had more pain, was more toxic and had a slightly higher temperature.

Operation.—Exploratory laparotomy was decided on, with a tentative diagnosis of obstruction of the common duct, possibly secondary to Weil's disease. It was thought that there was an inflammatory lesion in the common duct, particularly in the intramural part, which had caused a complete block either through inflammatory atresia or exudate. Calcium chloride was given intravenously for three days prior to operation. A transfusion of 500 cc. of blood was given the day prior to surgical intervention. On March 6 the operation was performed. The liver was observed to extend below the level of the umbilicus. The gallbladder was huge and extended well below the free border of the liver. The common duct was 3 or 4 cm. in diameter. The common duct was opened ¾ inch (2 cm.) from the cystic duct, and 1,500 cc. of bile was aspirated from the bile ducts. A probe was inserted into the distal portion of the common duct and was easily passed to the opening of the duct at the ampulla but could not be passed into the duodenum. There was evidently complete closure at that point due to growth of tissue. Choledochoduodenostomy was done.

Postoperative Course.—The patient left the operating room showing evidence of severe shock, as manifested by a pulse rate of 140 and a blood pressure of 74 systolic and 44 diastolic. The course following operation continued steadily down-

ward. There was continuous oozing of blood from the abdominal wound. Three blood transfusions did not affect the course. The patient died forty-nine hours after operation.

Autopsy.—The postmortem examination revealed that there was complete atresia of the intramural portion of the common bile duct, with great dilatation of the common duct, hepatic ducts and gallbladder. The anastomotic orifice of the com-

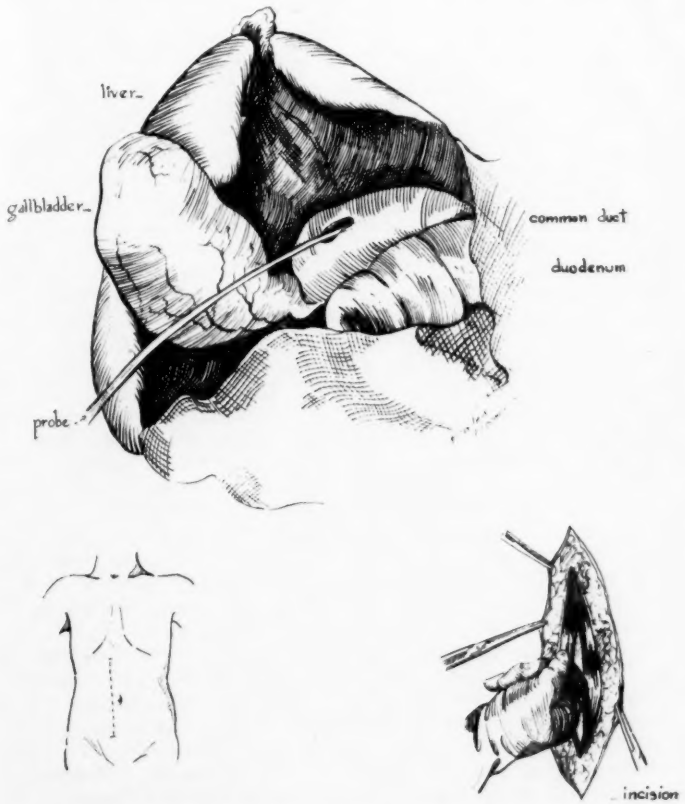


Fig. 2.—Weil's disease complicated by obstruction of the common duct.

mon duct into the duodenum was completely occluded by a large blood clot. The liver weighed 2,500 Gm. and was grossly normal, except that it was somewhat yellow. In the microscopic examination the hepatic cells showed cloudy swelling and scattered areas of focal necrosis. Sections stained by the Levaditi method revealed no organisms. Other diagnoses were: (1) bilateral bronchopneumonia, (2) focal necrosis of the spleen, (3) slight chronic glomerulonephritis and (4) slight biliary cirrhosis of the liver.

CASE 3.—J. E. M., a soldier aged 22, was admitted on April 19, 1935, with complaints of headache, vomiting and yellow discoloration of the eyes and skin. The patient had been perfectly well until the evening of April 15, when he suddenly became nauseated and vomited twice. The next two days he continued on duty but felt bilious; that is, he noted headache, anorexia, nausea and lack of energy. On April 17 he noticed that his eyeballs were yellow. Because of continuance of these symptoms he entered the hospital. There had been no abdominal pain or muscular cramps, and he had no other complaints.

Examination.—On admission to the hospital the patient was afebrile. He was well developed and well nourished but appeared acutely ill. His weight was 150 pounds (68 Kg.), compared with his usual weight of 160 pounds (72.6 Kg.). His height was 5 feet and 11 inches (180 cm.). The special senses were normal. The skin and mucous membranes showed moderate jaundice. There were no petechiae or hyperemia of the conjunctivae. There was no adenopathy. The tonsils were absent. The thyroid gland was normal. The pulse beats were equal, soft and regular. The blood pressure was 114 systolic and 76 diastolic. The heart and lungs were normal, as was also the genito-urinary system. Rectal examination revealed no abnormality, and the stools were of normal color. The abdominal examination revealed no abnormality. The liver and spleen were not palpable. The other systems were normal. There was no tenderness of the muscles of the calves.

Leptospiras were demonstrated in the blood by the dark field examination on the day the patient was admitted. A guinea-pig was inoculated with the patient's blood on April 26 and died on May 6. Autopsy of the animal showed a typical picture; leptospiras were demonstrated. The icterus index at the time of the patient's admission to the hospital was 14. The following week it reached its peak of 65 and was normal again after twelve weeks. The van den Bergh test gave a prompt direct reaction. On May 6 the serum bilirubin content was 6.5 van den Bergh units; on May 15 it was 3.2 units. On April 26 the Rosenthal hepatic function test showed 12 per cent retention after thirty minutes. In the fourth week of the patient's illness there was 15 per cent retention after thirty minutes. Weekly examinations from the fifth week on showed no thirty minute retention of the dye. On May 16 the nonprotein nitrogen content of the blood was 54 mg. The following week it was 60 mg., but thereafter it was normal. The cholesterol content of the blood was 162 mg. on May 16, 219 mg. on June 14 and 220 mg. on June 28. On entry the white blood cell count was 10,400, with 68 per cent polymorphonuclears, including 6 per cent eosinophils. Subsequent counts varied from 6,000 to 8,000, with from 3 to 6 per cent eosinophils. The red blood cell count, hemoglobin content and platelet count were normal, as were the bleeding and coagulation times. The Wassermann and Kahn reactions of the blood were negative. Fractional gastric analyses were normal. Urinalyses were normal except for a trace of albumin on occasions and also considerable bile. Specimens of urine were examined for organisms by the dark field method, but none were demonstrated.

Course.—The patient appeared to have a case of typical acute catarrhal jaundice, but owing to the recent study of a patient with Weil's disease in the hospital this patient's blood was examined by the dark field method and was found to contain leptospiras. For the fifteen dark field examinations made in this case no extended search was ever necessary. There were always from 10 to 30 organisms per high power field. Duodenal intubation was always successful in obtaining bile but without the usual changes in color concentration. The stools were light during the second week of hospitalization but always contained bile. The urine was at

times heavily bile stained. The patient remained completely afebrile throughout the entire period. Except for the initial complaints when admitted to the hospital, he felt well until about the fourth week. At that time pain developed over the right upper quadrant of the abdomen, and there was slight tenderness over the edge of the liver. However, there was no enlargement of the liver or spleen. The discomfort in the hepatic area gradually subsided and was not evident at the time of the patient's discharge. The jaundice persisted until the ninth week. For the first week there was some increase in the icterus, but thereafter it decreased rapidly until it was evident only in the conjunctivae. The patient never exhibited any evidence of a hemorrhagic diathesis.

The patient was placed on a diet high in carbohydrate and low in fat, augmented by syrup and daily ingestion of 1 quart (1 liter) of 10 per cent dextrose water. Alkaline mineral water was used. By June 18 the results of the hepatic function test of Rosenthal had been normal for the preceding five weeks, and the icterus index had approached normal. With this in mind and owing to the continued presence of leptospiras in the blood, we gave neoarsphenamine (0.3 Gm.) intravenously. On the following day and thereafter, leptospiras could not be demonstrated. Recovery appeared to be complete.

CASE 4.—M. K. I., a soldier aged 19, was admitted to the hospital on May 18, 1935, with chief complaints of pain in the right upper quadrant of the abdomen, muscular pains, malaise, headache and jaundice. He had been perfectly well until May 11, when malaise and anorexia developed and he vomited his supper. These symptoms continued, associated with progressive loss of energy. On May 14 he had a cramplike pain in the right upper quadrant of the abdomen, radiating into the left upper quadrant. The next day cramping pains developed in the muscles of the left calf. These muscular pains increased in severity and included both arms and both legs at the time of the patient's admission to the hospital. On May 16 he first noted that the stools were light and that the urine appeared dark. The following day a friend noticed yellowness of the patient's skin. There were no additional complaints.

Examination.—The patient was a well developed and well nourished jaundiced youth, appearing acutely ill. He was afebrile and ambulatory. His weight was 132 pounds (60 Kg.), and he was 5 feet and 7 inches (170 cm.) tall. The special senses were grossly normal. Both the skin and the mucous membranes were moderately jaundiced. Generalized slight lymphadenopathy was present, the tonsils were absent and the thyroid gland was slightly enlarged. The pulse beats were equal, soft and regular. The blood pressure was 118 systolic and 72 diastolic. The heart and lungs were normal, as was also the genito-urinary system. Rectal examination revealed no abnormality. The abdomen was soft, and there was slight prominence of the right upper quadrant owing to enlargement of the liver; the liver extended 3 fingerbreadths below the costal margin and was tender. The gallbladder and spleen were not palpable. There were no other masses. The nervous system, the osseous system and the muscles and joints were normal, except for marked tenderness of the muscles of the legs and arms to pressure.

When the patient was admitted the blood was examined in the dark field, and it was found teeming with leptospiras, as many as 20 to each high power field. The icterus index was 12.5 on May 18, 15.6 on May 23, 12.5 on May 27, 13.5 on June 1, 9 on June 7, 7.2 on June 11, 7.7 on June 17, 16.5 on June 22, 8.6 on June 26, 5 on July 8 and 4 on July 22. The Rosenthal hepatic function test showed 7 per cent retention after thirty minutes on May 22. On May 27 and June 1 there was no retention. On June 10 there was 5 per cent retention. From that date on there was no retention, the test being repeated weekly. The van den Bergh test

gave a prompt direct reaction. The white blood cell count ranged from 8,000 to 14,000, with a normal differential count and without any increase in the eosinophils. The red blood cell count, the bleeding and coagulation times and the hemoglobin content were normal. The stools were clay colored when the patient was admitted and remained light until August, when they again became dark. Urinalyses gave normal results, except for the presence of bile. Chemical analysis of the blood showed on May 20 66 mg. of nonprotein nitrogen and on May 23 54 mg.; thereafter the content was normal. On June 4 the cholesterol content was 192 mg.; on June 12, 200 mg., and on June 26, 178 mg. Other determinations of the cholesterol content both before and after these dates gave normal results. The Wassermann and Kahn reactions of the blood were negative. Gastric analyses by the fractional method showed high normal curves for acidity. A guinea-pig inoculated intraperitoneally with the patient's blood died in ten days and showed the typical evidence of Weil's disease. Leptospiras were recovered from this animal.

Course.—The patient was afebrile throughout the course of the illness, and at no time did he show any hemorrhagic tendencies. The stools remained light even after the icterus index had returned to normal. Repeated duodenal drainage resulted in the obtaining of light bile without the usual changes in color. Leptospiras were consistently and easily demonstrated in the patient's blood. On June 21 the patient was given intramuscularly 30 cc. of convalescent whole blood obtained from our third patient with Weil's disease. The following day there was a marked diminution in the number of organisms present in the patient's blood. From a previous average of from 10 to 20 per high power field, the number dropped to 5 per field. On this day 50 cc. of convalescent whole blood was again given intramuscularly, and thereafter organisms were not demonstrable in the patient's blood. Clinical improvement was also noticeable from this date. The patient stated that he felt improved and had more energy, less anorexia and less headache. There remained a subicteric tinge to the skin and scleras until the end of July. Recovery was slow but otherwise uneventful. The patient was returned to duty on August 21. It is to be noted that dark field examination of the blood was carried out weekly and leptospiras were easily demonstrated. This continued for the first five weeks of hospitalization, until a second injection of convalescent whole blood had been given.

Case 5.—G. C. D., a woman aged 42, was admitted on June 24, 1935. Her previous history showed rheumatic fever and chorea in childhood, and, except for an acute mental disturbance following the death of her husband in 1932, she had been apparently perfectly well until September 1934, nine months prior to her admission to the hospital, when she noticed swelling of the feet and ankles and moderate dyspnea on exertion. In May 1935 the patient's mother, from whom most of the history was obtained, noted a yellow cast to the patient's eyeballs and later a general yellow tinge of the skin. In the early part of June gastro-intestinal symptoms in the form of nausea and vomiting appeared. Little food was retained, and there was marked loss of weight and strength. Pain was not present at any time. Up to June 17 the patient had been under chiropractic treatment, but on this date the mother called a physician, and the patient was promptly sent to a hospital and treated mainly for congestive heart failure. A flat roentgenogram of the abdomen taken did not show gallstones. On June 24 the patient was transferred to this hospital. The tentative diagnosis of the physicians in charge was that of heart disease and possible carcinoma of the gallbladder or pancreas, the latter diagnosis being based mainly on the increasing painless jaundice.

Examination.—The patient appeared extremely ill. She was of normal development, with marked anasarca and jaundice. The skin was moist and cool, and there were several large ecchymotic spots on the arms, legs and back. There was no adenopathy. The pulse was decidedly irregular in force and rhythm but was soft. The blood pressure was 110 systolic and 70 diastolic. The heart was moderately enlarged by percussion both to the right and to the left. A systolic murmur was heard over the entire precordium but with maximum intensity over the apex. No thrill was palpable. Numerous coarse moist râles were scattered throughout both lungs. Moderately severe internal and external hemorrhoids were present. The edge of the liver was just palpable and was markedly tender. The tendon reflexes were absent. Pressure on the calves of the legs elicited severe pain.

On the day of the patient's admission to the hospital dark field examination of the blood revealed numerous leptospiras. They were also present on June 26. The icterus index was 90; on June 28 it was 81.8. The van den Bergh reaction was diphasic. On June 26 the Rosenthal hepatic function test showed 45 per cent retention of the dye after thirty minutes. The nonprotein nitrogen content of the blood was 31 mg., and the cholesterol content was 256 mg. All specimens of urine showed considerable albumin and bile, but leptospiras were not demonstrable. The red blood cell count was 5,100,000, and the hemoglobin content was 90 per cent (Tallqvist). The white blood cell count was 9,100, with a normal differential count. The platelet count was 255,000. The coagulation and bleeding times were normal. The Wassermann and Kahn reactions of the blood and spinal fluid were negative. The spinal fluid was icteric but was otherwise normal, and leptospiras could not be found. An electrocardiogram confirmed the clinical impression of auricular fibrillation.

Course.—At the time of admission to the hospital the patient was moribund, and she remained semicomatose and afebrile until death occurred on the sixth day. The treatment in this case was directed mainly toward the relief of cardiac failure. On June 26 she was given intramuscularly 25 cc. of convalescent serum from our fourth patient with Weil's disease, and while leptospiras were not again found in the blood, no other effect was noted. The clinical diagnosis was spirochetal jaundice and decompensated rheumatic mitral stenosis with auricular fibrillation.

Autopsy.—Autopsy revealed generalized ecchymosis of the skin and numerous submucosal and parenchymal petechiae. There was rheumatic mitral stenosis, the heart weighing 360 Gm. The liver was of normal size, yellowish gray and extremely soft and greasy. Microscopic examination of the liver showed severe midzonal fatty degeneration. The bile ducts and the duodenum were normal. An acute splenic tumor was present.

Case 6.—J. T. K., a soldier aged 34, was admitted on Feb. 6, 1931, for the treatment of active pulmonary tuberculosis. He was still a patient in this hospital with the tuberculosis well under control when, on May 30, 1935, epigastric discomfort developed. On June 20 it was noticed that he was jaundiced. There had been a loss in weight of 20 pounds (9 Kg.) in these three weeks. From June 23 to August 18 the patient had a low grade fever, the highest temperature being 100.2 F. and the average being 99 F. in the afternoons. The patient had not had any fever since shortly after his admission to the hospital in 1931. He was acutely ill, with marked abdominal discomfort associated with nausea and frequent vomiting from June 20 to July 9. Moderate, easily controllable epistaxis occurred several times during this period.

Examination.—The patient was well developed and well nourished but appeared acutely ill, with marked jaundice. He weighed 158 pounds (72 Kg.) and his

height was 5 feet and 11 inches (180 cm.). Phrenic exeresis and artificial pneumothorax were noted on the right side. The rest of the physical examination revealed only the presence of generalized abdominal tenderness. The liver, gallbladder and spleen were not palpable.

On June 25 dark field examination of the blood disclosed numerous leptospiras. Search of the urine, saliva and duodenal contents revealed no organisms. The white blood cell count varied from 4,400 to 6,500, with a normal differential count. The red blood cell count and hemoglobin content, as well as the coagulation and bleeding times, were normal. Urinalyses showed a faint trace of albumin several times during the febrile period and on one occasion several finely granular casts. The gastric analysis gave normal results. The Wassermann and Kahn reactions of the blood were negative. The van den Bergh test gave a prompt direct reaction.

The results of the other laboratory studies are shown in table 3.

Course.—On June 26 the patient was given intramuscularly 25 cc. of convalescent serum from our fourth patient with Weil's disease. From that date on no leptospiras were demonstrated in the blood. However, the patient continued

TABLE 3.—*Chemical Study of Blood of Sixth Patient*

Date	Nonprotein Nitrogen, Mg. per 100 Cc.	Cholesterol, Mg. per 100 Cc.	Bilirubin, Mg. per 100 Cc.	Icterus Index	Rosenthal Test, Retention in 30 Min., %
6/26	35	560	11	89	40
7/ 2	54	189	32	95	50
7/10	38	183	11	..	55
7/16	31	175	19	110	45
7/24	31	165	29	100	55
7/29	34	172	19	50	15
8/14	29	...	..	50	0
8/21	36	144	..	20	0
8/27	30	168	1	10	0
9/ 3	31	169	Normal	9	0
9/24	..	...	..	6	..
10/28	..	...	..	4	..

to be very ill for practically one month, with symptoms of severe hepatic damage. Recovery was eventually complete and without demonstrable effect on the tuberculous process.

CASE 7.—R. C. P., an officer aged 40, was admitted to the hospital on Nov. 7, 1934, with complaints of nausea, vomiting, weakness and epistaxis of two days' duration, associated with mild diarrhea.

Examination.—Physical examination revealed only slight jaundice and moderate tenderness over the gallbladder. The patient was thought to have a low grade infection of the gallbladder. The temperature was not elevated except on the first evening, when it was 100.8 F. The Graham-Cole test gave an abnormal response, in that the gallbladder did not empty well after the fatty meal. The other laboratory and roentgenographic studies gave normal results, except for an icterus index of 7.5.

Operation.—On December 5, with the patient under spinal anesthesia, cholecystectomy was performed. The gallbladder was of the usual white type. The glands along the cystic and common ducts were remarkably large. The ducts were normal, and no stones were present. General exploration revealed no abnormality. The pathologic report stated that section through the bulbous portion showed the unusual picture of a perfectly normal gallbladder, there being no erosion and no

evidence of old or recent inflammation, the mucosal fimbria being perfectly normal. Section near the outlet, however, showed a moderate fibrous infiltration but no recent inflammatory reaction.

Course.—The patient made an uneventful recovery and on Jan. 21, 1935, was discharged for one month's sick leave. He returned to duty on February 27. He stated at the time of discharge that he did not feel entirely normal. On July 1 he was readmitted to the hospital complaining that he had not felt perfectly well since his operation. He felt bilious; that is, he had anorexia, slight nausea, frequent headaches and lack of energy. At this time the patient was afebrile and slightly icteric. Dark field examination of the blood showed it teeming with leptospiras. The red blood cell count was 4,800,000, and the hemoglobin value was 85 per cent (Tallqvist). The bleeding and coagulation times were normal. The white blood cell count was 7,800, with a normal differential count. The icterus index on July 1 was 17.6; on July 5, 9.2, and on August 13, 12. The van den Bergh test showed a delayed direct reaction. The Rosenthal hepatic function test showed no retention of dye after either five or thirty minutes. On July 1 chemical analysis of the blood showed: nonprotein nitrogen, 75 mg.; cholesterol, 123 mg. and sugar, 92 mg. The urine, feces and sputum contained no leptospiras.

On July 2 the patient was given an intramuscular injection of 25 cc. of convalescent serum from our fourth patient with Weil's disease. On July 3 leptospiras were still demonstrable in the blood, but there were fewer than on the previous examination. On July 5 and thereafter, dark field examination revealed no organisms. This patient was returned to duty on August 13. He was not entirely recovered and complained of weakness and lack of energy. Various features of the case led to a neuropsychiatric consultation; the opinion was expressed that the patient showed an introverted personality but that no real neuropsychiatric pathologic condition was present. His wife's illness and the care of one child were undoubtedly features contributing to a certain amount of mental and physical depression in this case. While leptospiras were first discovered in July 1935, symptoms of a similar nature were noted eight months before this date. It is impossible to state definitely that Weil's disease was present when the patient was first admitted to the hospital, but the symptoms were suggestive. If leptospiras were present, then the duration of the disease in this case, as in our second case, was much longer than is ordinarily thought possible in Weil's disease.

SUMMARY

The pertinent literature on Weil's disease has been reviewed. The important symptoms of the thirteen patients previously reported on in North America and of our own series of seven patients are shown in table 1 and figure 1. The relationship of Weil's disease to infectious jaundice has been discussed. The diagnosis and treatment have been considered, with particular attention to our own results of treatment with neoarsphenamine intravenously and convalescent whole blood and serum intramuscularly. Reports on our seven patients are given. The most unusual feature was the typical painless obstructive jaundice of eight months' duration noted in our second patient at the time of his admission to the hospital. Operation and autopsy in this case revealed complete inflammatory atresia of the intramural portion of the common

bile duct secondary, presumably, to Weil's disease. The third patient showed an afebrile course, and leptospiras were demonstrable in the blood by dark field examination for nine weeks. Our fourth patient also was afebrile throughout, and leptospiras were demonstrable for five weeks. Our fifth patient appears to be the only woman with Weil's disease reported on in the North American literature, except in one instance of accidental laboratory infection.[8] Our seventh patient showed an afebrile course and was ambulatory for a period of eight months before the diagnosis was made; cholecystectomy was performed during this period without benefit.

CONCLUSIONS

The diagnosing of Weil's disease in seven cases, six of them being noted within a period of six months, indicates that this condition may not be rare.

Because of the fact that five of our patients showed an atypical course, according to the standard textbook picture, we believe that this disease should be considered more often when there is unexplained jaundice.

The source and mode of infection in these cases have not been determined. This is true not only for our series but also for the previously reported cases in North America, except for one instance of accidental laboratory infection.

BIBLIOGRAPHY

Aitken, A. B.; Connal, A.; Gray, G. M., and Smith, E. C.: Yellow Fever in Lagos During 1925, Tr. Roy. Soc. Trop. Med. & Hyg. **20**:166 (June) 1926.

Baermann, G., and Smits, E.: Diagnose, Klinik Epidemiologie und Therapie der Kurzfriestigen Weilschen Erkrankung, Centralbl. f. Bakt. (Abt. 1) **105**: 368, 1928.

——and Zuelzer, M.: Ueber die Aetiologie der Weilschen Krankheit, Klin. Wchnschr. **6**:979 (May 21) 1927.

Ball, Howard A.: Leptospiral Jaundice, Am. J. Clin. Path. **3**:283 (July) 1933.

Bates, J. E.: Leptospirosis Icterohemorragica (Weil's Disease), Canad. M. A. J. **16**:1466 (Dec.) 1926.

Blanchard, M.; Lefrou, G., and Laigret, J.: Spirochétose ictérigène épidémique observée sur des indigènes à Brazzaville, Bull. Soc. path. exot. **16**:184 (March 14) 1923.

Blumer, George: Infectious Jaundice in the United States, J. A. M. A. **81**:353 (Aug. 4) 1923.

Brown, H. C.: Serological Diagnosis of Weil's Disease, Brit. M. J. **1**:411 (March 2) 1935.

Buchanan, G.: Spirochetal Jaundice, Medical Research Council, Special Report Series, no. 113, London, His Majesty's Stationery Office, 1927.

Cushing, E. H.: Leptospirosis Icterohemorrhagica, J. A. M. A. **89**:1041 (Sept. 24) 1927.

Dawson, Bertrand; Hume, W. E., and Bedson, S. P.: Infective Jaundice, Brit. M. J. **2**:345 (Sept. 15) 1917.

Fairley, N. Hamilton: Weil's Disease Among Sewer Workers in London, Brit. M. J. **2**:10 (July 7) 1934.

Gaehtgens, W.: Beitrag zur Serodiagnose der Weilschen Krankheit, Klin. Wchnschr. **12**:697 (May 6) 1933.

Gay, Douglas Merrill, and Sellards, Andrew Watson: The Fate of Leptospira Icteroides and Leptospira Icterohemmorhagiae in the Mosquito, Aëdes Aegypti, Ann. Trop. Med. **21**:321 (Oct. 10) 1927.

Hayman, J. M., and Lynch, F. B.: Spirochetal Jaundice in the United States, Am. J. M. Sc. **173**:80 (Jan.) 1927.

Hindle, E., and White, P. B., in discussion on Schüffner.

Hübner, A., and Reiter, Hans: Beiträge zur Aetiologie der Weilschen Krankheit, Deutsche med. Wchnschr. **41**:1275 (Oct. 21) 1915; **42**:1 (Jan. 6); 131 (Feb. 3); 1282 (Oct. 19) 1916.

Ido, Y.; Hoki, R.; Ito, H., and Wani, H.: The Rat as a Carrier of Spirochaeta Ictero-Hemorrhagiae, the Causative Agent of Weil's Disease, J. Exper. Med. **26**:341 (Sept.) 1917.

Inada, Ryckichi: The Clinical Aspects of Spirochaetosis Ictero-Hemorrhagica or Weil's Disease, J. Exper. Med. **26**:355, 1917.

——Ido, Y.; Hoki, R.; Ito, H., and Wani, H.: Intravenous Serotherapy of Weil's Disease, ibid. **27**:283 (Feb.) 1918.

——Ido, Y.; Hoki, R.; Kaneko, R., and Ito, H.: The Etiology, Mode of Infection and Specific Therapy of Weil's Disease (Spirochaetosis Icterohemorrhagica), ibid. **23**:377 (March) 1916.

Jeghers, Harold J.; Houghton, John D., and Foley, John A.: Weil's Disease, Arch. Path. **20**:447 (Sept.) 1935.

Jobling, J. W., and Eggstein, A. A.: The Wild Rats of the Southern States as Carriers of Spirochaeta Icterohemorrhagiae, J. A. M. A. **69**:1787 (Nov. 24) 1917.

Langworthy, Virginia, and Moore, Anna C.: A Study of Leptospira Icterohemorrhagiae, J. Infect. Dis. **41**:70 (July) 1927.

Lusena, M., and Carlinfanti, E.: Antigéne pour le diagnostic serologique de la spirochétose icterohemorrhagique, Soc. internaz. di microbiol., Boll. d. sez. ital. **6**:77 (March) 1934.

Lyon, D. M., and Buchanan, G.: Spirochetal Jaundice: Report of a Small Epidemic, Lancet **1**:504 (March 7) 1925.

McDowell, E. S.: A Case of Infectious Jaundice, New York State J. Med. **25**:19 (Jan. 16) 1925.

Manteufel, P.: Vereinfachung des Züchtungsverfahrens von Weil Spirochäten, Deutsche med. Wchnschr. **47**:461, 1921.

Mulholland, H. B., and Bray, W. E.: Spirochetal Jaundice, J. A. M. A. **90**:1113 (April 7) 1928.

Neill, M. H.: The Problem of Acute Infectious Jaundice in the United States, Pub. Health Rep. **33**:717 (May 10) 1918.

Noguchi, Hideyo: Spirochaeta Icterohemorrhagiae in American Wild Rats and Its Relation to the Japanese and European Strains, J. Exper. Med. **25**:755 (May 1) 1917.

Morphological Characteristics and Nomenclature of Leptospira (Spirochaeta) Icterohemorrhagiae, ibid. **27**:575 (May) 1918.

Etiology of Yellow Fever, ibid. **30**:401 (Oct.) 1919.

Otteraaen, Andrew: The Spirochete of Infectious Jaundice (Spirocheta Icterohemorrhagiae, Inada; Leptospira, Noguchi) in the House Rats in Chicago, J. Infect. Dis. **29**:485 (May) 1919.

Reiter, Hans: Beiträge zur Aetiologie der Weilschen Krankheit, Deutsche med. Wchnschr. **42**:1282 (Oct. 19) 1916.

Sailor, Joseph: Leptospirosis Icterohemorrhagica (Weil's Disease), Am. J. M. Sc. **170**:332 (Sept.) 1925.

Schüffner, W.: Recent Work on Leptospirosis, Tr. Roy. Soc. Trop. Med. & Hyg. **28**:7 (June) 1934.

——and Mochtar, A.: Gelbfieber und Weilsche Krankheit, Arch. f. Schiffs- u. Tropen-Hyg. **31**:149 (April) 1927.

Schürer, J.: Weil's Disease as the Result of an Accident, Med. Klin. **18**:533 (April 23) 1922.

Stirl, Otto: Zur Lehre von der infectiösen fieberhaften, mit Icterus complicirten Gastroenteritis (Weil'sche Krankheit), Deutsche med. Wchnschr. **15**: 798 (Sept. 26) 1889.

Stokes, A.; Ryle, J. A., and Tytler, W. H.: Weil's Disease in the British Army in Flanders, Lancet **1**:142 (Jan. 27) 1917.

Towler, Harry H., and Walker, John E.: Spirochetal Jaundice, J. A. M. A. **89**:86 (July 9) 1927.

Uhlenhuth, Paul, and Fromme, W.: Experimentelle Untersuchungen über die sogenannte Weilsche Krankheit, Med. Klin. **11**:1202 (Oct. 31); 1264 (Nov. 14); 1296 (Nov. 21); 1375 (Dec. 12) 1915.

Weilsche Krankheit, in Kolle, W.; Kraus, R., and Uhlenhuth, P.: Handbuch der pathogenen Mikroorganismen, Jena, Gustav Fischer, 1930, vol. 7, pt. 1, p. 487.

——and Kuhn, P.: Experimentelle Uebertragung der Weilschen Krankheit durch die Stallfliege, Ztschr. f. Hyg. u. Infectionskr. **84**:517, 1917.

——and Zuelzer, M.: Zur Epidemiologie der Weilschen Krankheit: Zugleich ein Beitrag zur Frage der freilebenden Spirochäten (icterogenesähnlichen und andere), Centralbl. f. Bakt. (Abt. 1) **85**:141 (Feb. 28) 1921; cited by Topley, W. W. C., and Wilson, G. S.: The Principles of Bacteriology and Immunity, ed. 1, Baltimore, William Wood & Company, 1929, vol. 2.

Wadsworth, Augustus; Langworthy, Virginia H.; Stewart, Constance F.; Moore, Anna C., and Coleman, Marion B.: Infectious Jaundice Occurring in New York State, J. A. M. A. **78**:1120 (April 15) 1922.

Weil, Adolph: Ueber eine eigenthümliche, mit Mitztumor, Icterus und Nephritis einhergehende, acute Infektionskrankheit, Deutsches Arch. f. klin. Med. **39**: 209 (July 28) 1886.

Wolbach, S., and Binger, L.: J. M. Research **30**:23, 1914.

INFLUENCE OF FAT ON CONCENTRATION OF SUGAR IN BLOOD AND IN URINE IN DIABETES MELLITUS

MAX WISHNOFSKY, M.D.

ARTHUR P. KANE, M.D.

AND

WILLIAM C. SPITZ, M.D.

BROOKLYN

The discovery of insulin brought about a revolution in the dietary management of diabetes mellitus. Whereas in the preinsulin era the low carbohydrate-high fat diet was universally employed, now the majority of authorities advocate the high carbohydrate-low fat diet. Indeed, the revolution has been even more marked. In the preinsulin era carbohydrate was considered the *bête noire* of diabetic patients; now this rôle has been assigned by some investigators to fat. The advent of insulin made possible the discovery of certain fundamental principles of the metabolic disturbance in diabetes mellitus. The subject, however, is still to a large degree in a bedeviled and controversial state. In this paper the literature of the subject will be reviewed and discussed, and some experimental work will be reported.

In 1923 Allen [1] reported the results of an exhaustive study of this subject with a large number of patients and stated the following fundamental conclusions: 1. Fat causes glycosuria out of all proportion to the dextrose content. It seems important chiefly through the number of calories which it furnishes rather than as a theoretical source of dextrose. 2. This action of fat is most prompt and obvious in the cases of severest involvement; in cases of mild diabetes it may take weeks or months to make its appearance. 3. The insulin requirement of the organism is governed not only by carbohydrate but by fat and all other elements entering into the diet. 4. It remains uncertain whether insulin is directly concerned in total metabolism or specifically related to the assimilation of dextrose alone and only in some secondary or indirect manner with the metabolism of other foods.

From the Clinic for Diabetic Patients, the Department of Basal Metabolism and the Department of Medicine of the Jewish Hospital.

1. Allen, F. M.: Influence of Fat and Total Calories on Diabetes and the Insulin Treatment, J. Metabolic Research **3**:61, 1923.

Adlersberg and Porges [2] have written extensively on this subject during the past decade. Their concept is based on the theory that ingestion of large quantities of fat causes infiltration of the hepatic cells with fat and that a fatty liver can less easily take up dextrose to form glycogen than a glycogen-rich liver. They stated that a diet poor in carbohydrate increases the activity of the pancreas and gives rise to an improvement in tolerance for carbohydrate. Experimentally they demonstrated the following facts: 1. Addition of fat to a maintenance diet causes a marked increase in glycosuria which takes days to develop. 2. Equicaloric substitution of carbohydrate for fat in a diet improves the tolerance of the diabetic patient and makes the insulin requirement less. 3. The conception that undernutrition improves the tolerance and that overnutrition lowers it is untenable. Overnutrition with fat reduces the tolerance, but such is not the case with carbohydrate.

Of great importance is the finding that equicaloric (Adlersberg and Porges [2] and Gray and Sansum [3]) or equigram (Richardson [4]) substitution of carbohydrate for fat may be carried out without causing an increase in insulin requirement, and at times it may even permit a reduction in the dosage. Richardson [4] has stated: "Carbohydrate seems to use insulin for its own metabolism, but whether fat also uses insulin for this purpose, or whether it in some way inhibits the use of the insulin by the carbohydrate we do not know." Barach [5] has expressed the opinion that 1 Gm. of fat creates the need for as much insulin as 2 Gm. of carbohydrate.

There are eminent students of the disease who entertain opinions which are diametrically opposed to those just presented. Thus, Newburgh and Waller [6] have presented studies from which they concluded

2. Adlersberg, D., and Porges, O.: Zur Theorie und Praxis der kurativen Diabetesbehandlung, Klin. Wchnschr. **5**:1451, 1926; Weitere Erfahrungen über die Behandlung des Diabetes mellitus mit fettarmer Diät, ibid. **6**:2371 (Dec. 10) 1927; Ueber die Diätbehandlung der Zuckerkrankheit mitt fettarmer Kost: Kohlehydrat-Mastkuren bei unterernährten Zuckerkranken, ibid. **7**:1503 (Aug. 5) 1928. Adlersberg, D.: Fettreiche oder fettarme Ernährung des Diabetikers? Zentralbl. f. inn. Med. **53**:401 (April 2) 1932. Adlersberg, D., and Porges, O.: Ueber kurzfristige Behandlung der Zuckerkrankheit mit fettarmer, kohlehydratreicher Kost unter gleichzeitiger Insulinanwendung, Med. Klin. **28**:1386 (Sept. 30) 1932.

3. Gray, P. A., and Sansum, W. D.: Higher Carbohydrate Diet Method in Diabetes Mellitus, J. A. M. A. **100**:1580 (May 20) 1933.

4. Richardson, R.: High-Carbohydrate Diets in Diabetes Mellitus, Am. J. M. Sc. **177**:426, 1929.

5. Barach, J. H.: Lower Fat Diet in Diabetes, J. A. M. A. **98**:1265 (April 9) 1932.

6. Newburgh, L. H., and Waller, D. S.: Studies of Diabetes Mellitus: Evidence That Disability Is Concerned Solely with Metabolism of Glucose, J. Clin. Investigation **11**:995, 1932.

that the ability of a diabetic patient to dispose of the available dextrose of a diet is unrelated to either the fat or the total energy content of the diet. This holds for long and for short periods of experimentation. Falta [7] has rejected the contention that the tolerance improves only with a low fat-high carbohydrate diet. He has claimed that an equal improvement can occur with a high fat-low carbohydrate diet.

The protagonists of the high carbohydrate-low fat diet have laid great stress on the fact that if a normal person is placed on a pure fat diet for several days a dextrose tolerance test performed immediately afterward shows a blood sugar curve which is higher than normal. Indeed, this is one of the most important arguments advanced by Adlersberg and Porges [8] for their conception of the metabolic disturbance in diabetes mellitus. Himsworth [9] found that the administration to a normal rabbit of a diet rich in fat decreases the sugar tolerance, retards and diminishes the action of insulin on the blood sugar, prevents or delays the progressive improvement of sugar tolerance which occurs with the injection of consecutive doses of dextrose and impairs the ability of insulin to diminish the hyperglycemia following the intravenous injection of dextrose. It seems to us that this argument is not well founded and cannot be applied to diabetes mellitus for the following reason: It is well established that a dextrose tolerance test will show an elevated blood sugar curve in normal persons after fasting equal to that of normal persons who have been receiving a high fat diet. Starvation, however, instead of producing a depreciation of tolerance for carbohydrate in diabetic patients, causes an increase. Fasting constituted a basic method of treatment of diabetes in the preinsulin era. This, it appears to us, is cogent evidence that it is fallacious to apply results of experiments on normal persons to diabetic patients. MacKay and Bergman [10] found that in the rat a preceding diet composed chiefly of fat was without influence on subsequent deposition of glycogen in the liver or muscles.

Of late there has been a renewal of interest in the influence of fat on the blood sugar level during fasting. Hirsch-Kauffmann and Knauer [11] found that administration of fat (50 cc. of olive oil) to normal children

7. Falta, W.: Ueber die Frage der Fettzufuhr in der Diabetesbehandlung, Wien. med. Wchnschr. **82**:1291 (Oct. 8) 1932.

8. Adlersberg, D., and Porges, O.: Fettnahrung und Kohlehydrattoleranz, Med. Klin. **27**:1783 (Dec. 4) 1931.

9. Himsworth, H. P.: Dietetic Factors Influencing Glucose Tolerance and Activity of Insulin, J. Physiol. **81**:29 (March 29) 1934.

10. MacKay, E. M., and Bergman, H. C.: The Influence of the Preceding Diet upon the Rate of Glucose Absorption and Glycogen Synthesis, J. Nutrition **6**:515, 1933.

11. Hirsch-Kauffmann, H., and Knauer, H.: Ueber den Einfluss von Kohlehydrat- und Fettzufuhr auf Glykämie und Lipoidstoffwechsel, Med. Klin. **29**:562 (April 21) 1933.

gave rise to a blood sugar curve similar to that produced by the administration of dextrose. On the contrary, Jacobsen,[12] Petrén,[13] Paasch and Schönfeld[14] and Depisch and Hasenöhrl[15] have found that the ingestion of fat does not in the slightest influence the blood sugar level of normal persons during fasting. Schönfeld[16] has even found that the administration of fat to children produces a reduction in the blood sugar level during fasting. Study of this subject in diabetes has been slight. Hirsch-Kauffmann and Knauer[11] found a rise in the blood sugar of diabetic children after the administration of 50 cc. of olive oil. Paasch and Schönfeld[14] in one case and Depisch and Hasenöhrl[15] in two cases found no change or the usual drop in sugar concentration which occurs in diabetic patients during the day while fasting.

Depisch and Hasenöhrl[15] have found further that the blood sugar curve for normal persons after the injection of insulin is not as low after the administration of fat as when no fat is given. They also found that the blood sugar curve for normal persons after the administration of dextrose is lower than when dextrose plus fat is given. They concluded that fat inhibits the action of both endogenous and exogenous insulin. Schur and his associates[17] noted that the administration of insulin caused an increased deposition of fat after the feeding of fat to normal animals. They concluded that fat excites the secretion of insulin just as does carbohydrate, though to a lesser degree.

Joslin[18] in his latest textbook has stated that insulin is concerned not only with the metabolism of dextrose but with that of protein and fat.

RATIONALE OF EXPERIMENTS

In this paper several experiments will be described which were performed for the purpose of determining the relationship between insulin and the metabolism of fat in diabetes mellitus. It is first necessary

12. Jacobsen, T. B.: Untersuchungen über den Einfluss verschiedener Nahrungsmittel bei normalen, zuckerkranken und graviden, Personen, Biochem. Ztschr. **56**:471, 1913.

13. Petrén, K.: Studien über die Faktoren, welche bei gesunden Individuen und bei Diabetikern auf die Blutzuckerkurve einem Einfluss ausüben, Arch. f. exper. Path. u. Pharmakol. **99**:52, 1923.

14. Paasch, G., and Schönfeld, H.: Ueber den Ablauf der Blutzuckerkurve nach Fettbelastung, Monatschr. f. Kinderh. **59**:181, 1934.

15. Depisch, F., and Hasenöhrl, R.: Weiterer Beitrag zur Blutzuckerregulation, Fett- und Kohlehydratstoffwechsel, Klin. Wchnschr. **8**:202 (Jan. 29) 1929.

16. Schönfeld, H.: Zur Frage der Blutzuckerbeeinflussung durch perorale Fettzufuhr, Monatschr. f. Kinderh. **61**:432, 1935.

17. Schur, H.; Löw, A., and Krčma, A.: Die Wirkung des Insulins auf die provisorische Unterbringung resorbierter Kohlehydrate und Fette im Organismus, Wien. Arch. f. inn. Med. **25**:203, 1934.

18. Joslin, E. P.; Root, H. F.; White, P., and Marble, A.: The Treatment of Diabetes Mellitus, ed. 5, Philadelphia, Lea & Febiger, 1935, p. 17.

to take cognizance of the following points: The metabolism of fat may be considered from two standpoints: (1) deposition in tissues and (2) oxidation. That there is no defect in the oxidation of fat even in the most severe stages of diabetes has been proved beyond doubt. Insulin, therefore, is certainly not necessary for the oxidative metabolism of fat. If it is at all concerned with the metabolism of fat, it would be only with its deposition in the tissues.

The action of insulin, as contrasted with that of thyroid, is immediate in onset and lasts for only several hours. Any action of insulin will make itself evident during this period. Any phenomenon which makes its appearance several days or weeks later certainly cannot be ascribed to insulin.

The pathologic physiology of diabetes mellitus is not understood in its entirety, but certainly one important factor is hypo-insulinism. The administration of an excessive, definite dose of dextrose to a diabetic patient will engender the maximum secretion of insulin of which he is capable. A blood sugar curve of a certain height and length will be obtained. If a large amount of fat is given with the same dose of dextrose to the same patient, assuming that fat requires insulin for storage, less insulin would therefore be available for the metabolism of the dextrose, for when the dextrose is given alone the secretion of insulin is at its maximum. It is logical, therefore, to assume that the blood sugar curve would be higher and the glycosuria more marked. If, however, fat does not require insulin for its storage, then the curves for sugar in the blood and in the urine would be identical with those obtained when dextrose is given alone.[19]

A study of the influence of fat on the blood sugar level of diabetic patients during fasting would be necessary in order to corroborate the aforementioned results. It is logical to assume that if fat requires insulin for its utilization, a rise should occur, whereas if insulin is not concerned with the metabolism of fat the value would remain unchanged.

The results obtained from a study of the influence of fat on the blood sugar level of normal persons during fasting are not necessary for our argument. However, in view of the fact that there is a diversity of opinion on this subject, it was decided to include this work in our studies.

METHOD OF PROCEDURE

GROUP 1: *Diabetic Patients Receiving Dextrose and Dextrose Plus Fat.*—Experiments were performed on eleven diabetic patients. To each of them 60 Gm.

19. It has been shown (Wishnofsky, M., and Kane, A. P.: Am. J. M. Sc. **189**:545, 1935) that if equivalent amounts of dextrose and starch are given to a diabetic patient two days apart, the curves for the sugar contents of the blood and urine will be identical. It is reasonable to assume that the same will hold true if equal quantities of dextrose are given two days apart.

of dextrose in a 20 per cent aqueous solution was given in the morning after a fast of fourteen hours. Specimens of blood (venous) were taken at the fasting level, immediately before ingestion, one and one-half and three hours after the ingestion of the dextrose. The sugar content of the blood was determined by the Folin-Wu method. Urine was collected one and one-half, three and six hours after the ingestion of dextrose, and its sugar content was determined by the Benedict method.

Two days later, also in the morning after a fast of fourteen hours, 60 Gm. of dextrose in a 20 per cent aqueous solution was given, immediately followed by 120 Gm. of olive oil.[20] The specimen of blood was taken, and the urine was collected at the same periods as when dextrose alone was given. In the interval between tests the patients received their customary diets. Those who had been taking insulin continued to do so.

TABLE 1.—*Concentration of Dextrose in Blood and Quantity of Dextrose in Urine of Diabetic Patients After Ingestion of Dextrose and of Dextrose and Olive Oil* *

	Sugar, Mg. per 100 Cc. of Blood						Sugar, Gm. per 100 Cc. of Urine					
	Fasting Level		90 Min. Post Cibum		3 Hr. Post Cibum		0 to 90 Min. Post Cibum		90 Min. to 3 Hr. Post Cibum		4 to 6 Hr. Post Cibum	
Case Number	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat	Dextrose	Dextrose and Fat
1	174	182	400	368	268	370	10.3	4.6	15.3	13.0	2.4	4.6
2	242	244	400	380	286	267	13.6	9.0	12.4	9.0	1.5	1.6
3	133	110	488	429	364	292	3.3	2.8	7.2	5.9	1.1	0.9
4	259	258	444	310	320	235	6.4	4.0	12.3	4.6	1.1	3.4
5	237	210	465	424	313	320	10.3	7.8	10.4	11.4	2.0	3.3
6	228	235	382	348	258	328	9.0	5.2	....	....	0.7	0.6
7	275	278	550	500	484	392	7.9	8.5	12.9	11.8	9.6	10.2
8	217	236	448	438	338	360	7.2	3.7	8.9	11.6	3.2	1.6
9	354	354	571	571	465	571	11.1	5.7	14.1	12.0	7.3	6.7
10	330	300	494	374	381	388	12.0	9.5	18.6	17.2	10.3	6.2
11	220	217	317	313	333	292	3.6	2.5	4.2	5.1	3.5	1.8
Average	243	239	451	405	348	347	8.6	5.75	11.7	10.15	3.88	3.72

* Sixty grams of dextrose and 60 Gm. of dextrose plus 120 Gm. of olive oil were ingested.

GROUP 2: *Diabetic Patients Receiving Fat Only.*—Experiments were performed on thirteen diabetic patients. To each of them 120 Gm. of olive oil was given in the morning after a fast of fourteen hours. Specimens of blood (venous) were taken at the fasting level immediately before the ingestion and one, two and three hours after the ingestion of olive oil. The sugar content of the blood was determined by the Folin-Wu method.

GROUP 3: *Normal Persons Receiving Fat Only.*—Experiments were performed on ten normal persons. The procedure was identical with that for group 2.

ANALYSIS OF RESULTS

GROUP 1: *Diabetic Patients Receiving Dextrose and Dextrose Plus Fat.*—In table 1 are recorded the concentrations of blood sugar and the amounts of dextrose in the urine after the ingestion of dextrose and

20. Olive oil is 100 per cent fat.

after the ingestion of dextrose and fat. Statistical analysis [21] reveals the following facts: 1. There is no significant difference in the concentrations of the blood sugar at the fasting level. 2. The concentration of the blood sugar is significantly greater one and one-half hours after the ingestion of dextrose than after the ingestion of dextrose and fat. This holds true also for the dextrose in the urine for ninety minutes post cibum. 3. There is no significant difference in the concentrations of dextrose in the blood three hours post cibum or in the dextrose in the urine from one and one-half to three hours and from four to six hours, inclusive, post cibum.

In a previous paper we [22] stated our conclusion that fat does not influence the absorption of dextrose from the alimentary canal of human beings. The difference at the one and one-half hour level post cibum

TABLE 2.—*Concentration of Dextrose in Blood of Diabetic Patients at Fasting Level and After Ingestion of 120 Gm. of Olive Oil*

Case Number	Sugar, Mg. per 100 Cc. of Blood			
	Fasting Level	1 Hr. Post Cibum	2 Hr. Post Cibum	3 Hr. Post Cibum
1	256	260	235	196
2	183	183	177	156
3	263	260	249	238
4	280	263	230	200
5	225	207	176	182
6	274	280	268	262
7	160	165	147	138
8	220	222	180	176
9	318	288	281	263
10	187	198	196	187
11	173	187	166	156
12	183	181	167	152
13	148	148	125	124

may be interpreted as an initial reduction in the rate of absorption of dextrose as a result of the retardation of the emptying of the stomach. For our purposes the important conclusion is that a large amount of fat does not increase the glycemia and glycosuria produced in diabetic patients by a definite dose of dextrose.

GROUP 2: *Diabetic Patients Receiving Fat Only.*—In table 2 are recorded the concentrations of dextrose in the blood of thirteen diabetic patients at the fasting level and one, two and three hours after the ingestion of 120 Gm. of olive oil. Vesa [23] has well described the drop in blood

21. The method of analysis used was that developed by R. A. Fisher (Statistical Methods for Research Workers, ed. 3, London, Oliver & Boyd, 1930, p. 104).

22. Wishnofsky, M.; Kane, A. P., and Spitz, W. C.: The Influence of Fat on the Absorption of Dextrose from the Human Alimentary Canal, Am. J. Digest. Dis. & Nutrition **4**:174 (May) 1937.

23. Vesa, A.: Studien über Diabetes mellitus unter Anwendung von zweistündlichen bei Tag und Nacht entnommenen Blutzucker- und Harnproben, Acta med. Scandinav., supp. 57, 1934, p. 1.

sugar level which occurs during the day in fasting diabetic patients. This was noted in our patients and was in no way influenced by the ingestion of fat.

GROUP 3: *Normal Persons Receiving Fat Only.*—In table 3 are recorded the concentrations of dextrose in the blood of ten normal persons at the fasting level and one, two and three hours after the ingestion of 120 Gm. of olive oil. The concentration of dextrose is not influenced by the ingestion of fat.

COMMENT

In the review of the literature it was brought out that a strong impression exists that insulin is intimately concerned with the metabolism of fat. To recapitulate: 1. Allen has stated that insulin is either directly or in some secondary and indirect manner concerned with the metabolism

TABLE 3.—*Concentration of Dextrose in Blood of Normal Persons at Fasting Level and After Ingestion of 120 Gm. of Olive Oil*

	Sugar, Mg. per 100 Cc. of Blood			
Case Number	Fasting Level	1 Hr. Post Cibum	2 Hr. Post Cibum	3 Hr. Post Cibum
1	107	90	84	86
2	122	105	103	100
3	93	95	91	95
4	90	86	93	95
5	90	87	90	..
6	90	87	83	91
7	87	81	80	85
8	81	82	91	95
9	100	95	95	100
10	85	100	95	100

of fat. 2. Richardson has claimed that fat uses insulin for its own metabolism or in some way inhibits the use of insulin by carbohydrate. 3. Barach has stated that 1 Gm. of fat creates the need for as much insulin as 2 Gm. of carbohydrate. 4. Joslin has stated that insulin is just as much concerned with the metabolism of fat and protein as with that of carbohydrate. 5. Depisch and Hasenöhrl have stated as their conclusion that fat inhibits the action of both endogenous and exogenous insulin. 6. Schur and his associates have claimed that the administration of fat excites the secretion of insulin just as does carbohydrate, though to a lesser degree. 7. Himsworth has stated as his conclusion that fat retards and diminishes the action of insulin on the blood sugar.

It is important to reiterate that in the study of the relationship between insulin and the metabolism of fat the two following factors are of fundamental importance: 1. Insulin is not necessary for the oxidation of fat. It can be concerned, if at all, only with the deposition of fat in the tissues. 2. The action of insulin is immediate in onset and of

short duration. Any phenomena which appear days or weeks later cannot be ascribed to insulin.

A definite answer to this problem, namely, the influence of insulin on the metabolism of fat, can be obtained from the experiments herein described. Sixty grams of dextrose was given to each of a series of diabetic patients. The dextrose contents of the blood and urine were studied for a sufficiently long period, namely, six hours. The insulin response to this dose may be considered maximum. Two days later 60 Gm. of dextrose was given with 120 Gm. of fat. This amount of fat, given as a single dose, may be considered large. If fat required insulin for its storage it would make less insulin available for the metabolism of the dextrose, and a significant increase in the dextrose contents of the blood and urine should occur. But over a period of six hours this result did not occur. The important conclusion is that fat does not require insulin for its metabolism; for the same reason, it does not inhibit or retard the action of insulin. Allen [1] and Adlersberg and Porges [2] have shown that the addition of considerable fat to a maintenance diet produces a depreciation of the tolerance of the diabetic patient for carbohydrate. This action makes its appearance only after days or weeks of increased feeding of fat. Their results are convincing. However, the mechanism producing this change must, in the present state of knowledge, be considered unknown.

The work on the influence of fat on the blood sugar level of diabetic patients during fasting has been fragmentary. We have studied this action in a series of thirteen diabetic patients and have found that a large dose of fat does not in the slightest prevent the fall in blood sugar level which occurs during the day in diabetic patients during fasting. The results do not have the critical value of those just described; they tend, however, to corroborate the conclusions drawn.

Large doses of fat do not influence the fasting level of the blood sugar of normal persons. This finding is in agreement with that of most investigators.

SUMMARY AND CONCLUSIONS

A review of the literature is given. A strong impression exists that insulin is intimately concerned with the metabolism of fat. Experiments are presented from which it is concluded that fat does not require insulin for its metabolism and that it does not inhibit or retard the action of insulin. Incidentally, it is shown that the ingestion of large amounts of fat does not influence the fasting level for blood sugar of diabetic patients or normal persons.

CHRONIC ARSENICAL POISONING DURING THE TREATMENT OF CHRONIC MYELOID LEUKEMIA

E. V. KANDEL, M.D.*
AND
G. V. LEROY, M.D.
CHICAGO

The value of inorganic arsenical preparations in the treatment of chronic myeloid leukemia was neglected in the American medical literature from the time that roentgen therapy was suggested by Nicholas Senn [1] until the report of Forkner and Scott [2] in 1931. The 1931 report described a favorable reaction in nine of ten patients receiving solution of potassium arsenite in subtoxic amounts. Later Forkner [3] described its successful use in eighteen patients, none of whom had received the drug for longer than one year. In 1936 Stephens and Lawrence [4] reported on seven patients treated successfully for about four years or less. The early authors encountered no complications more serious than transient conjunctivitis, coryza, nausea and diarrhea. One patient had herpes zoster while taking arsenic, but the authors considered that this was as likely to be a feature of the leukemia as a result of the treatment. One of the patients exhibited generalized pigmentation of the skin after several months of arsenic medication, but no other complications were observed. All three papers by Forkner and Scott, and Stephens and Lawrence contained allusions to the possibility of more serious hepatic, renal or cutaneous lesions from prolonged ingestion of arsenic.

In this paper we wish to describe the course and necropsy observations in a case of chronic myeloid leukemia in which the patient was given intensive treatment with solution of potassium arsenite and roent-

* Douglas Smith Foundation Research Fellow.
From the Department of Hematology, the University of Chicago.

1. Senn, N.: Case of Splenomedullary Leukaemia Successfully Treated by the Use of Röntgen Ray, M. Rec. **44**:281, 1903.

2. Forkner, C. E., and Scott, T. F. M.: Arsenic as a Therapeutic Agent in Chronic Myelogenous Leukemia, J. A. M. A. **97**:3-5 (July 4) 1931.

3. Forkner, C. E.: The Administration of Solution of Potassium Arsenite in the Treatment of Chronic Myelogenous Leukemia, M. Clin. North America **15**: 1057-1064, 1932.

4. Stephens, D. J., and Lawrence, J. S.: The Therapeutic Effect of Solution of Potassium Arsenite in Chronic Myelogenous Leukemia, Ann. Int. Med. **9**:1488-1502, 1936.

gen therapy and in whom cutaneous and hepatic lesions due to the arsenic developed. Briefer notes on the results of arsenic therapy in five other patients with chronic myeloid leukemia who showed certain features of this form of treatment are included.

REPORT OF CASES

CASE 1.—A 61 year old Jew, single, formerly a chauffeur, entered the University of Chicago Clinics on Aug. 18, 1931. He had had a brownish blotchy discoloration of the skin of the trunk for about fifteen years. Two years prior to his admission to the clinic progressive enlargement of the lymph nodes, asthenia, dyspnea, cough and epistaxis commenced. In the winter of 1930 a diagnosis of leukemia was made; the leukocyte count then was 64,000, and he was given twenty roentgen treatments, of unknown dosage, over the enlarged lymph nodes. This helped but little, and in August 1931 the leukocyte count was 24,000. One week before coming to the clinic he was given by a physician solution of potassium arsenite in increasing doses. On the day of registration the patient was taking 13 minims (0.8 cc.) three times a day and was experiencing headache, nausea and vomiting for the first time. His past history and family history were irrelevant. His health and habits had been excellent.

Physical examination disclosed a thin, poorly nourished man with large, irregular brawny red blotches on the skin of the trunk and limbs. The heart was not enlarged. The blood pressure was 160 systolic and 90 diastolic. There was general arteriosclerosis of grade 2. The liver was palpable 15 cm. below the right costal margin in the midclavicular line[5]; it was of normal consistency and tender. The spleen was relatively small and firm. It was easily felt protruding just below the left costal margin and was not tender. There was pitting edema of grade 2 of the legs from the groin downward. Varicosities were present on both legs. The prostate gland was enlarged and tender, and the expressed fluid contained much pus. All the superficial lymph nodes were enlarged, varying in size from that of a pea to that of a hazelnut. They were discrete, firm and nontender. The Wassermann reaction of the blood was negative. Examination of the urine revealed no abnormality. The blood count showed: hemoglobin, 11.5 Gm.; erythrocytes, 4,200,000, and leukocytes, 7,600. The differential count showed: myelocytes, 11 per cent; metamyelocytes, 4 per cent; polymorphonuclears, 68 per cent; lymphocytes, 12 per cent; monocytes, 4 per cent, and normoblasts, occasional.

The diagnosis was chronic myeloid leukemia; arteriosclerotic heart disease, with congestive heart failure of grade 2b, and chronic prostatitis.

Course.—Chart 1 presents the variations in the leukocyte count, the doses of solution of potassium arsenite and the dates of the roentgen treatments. Throughout the entire illness the hemoglobin value and the red cell count were easily maintained at a good level with occasional courses of iron medication. The leukocyte count was kept at reasonable levels by the persistent administration of solution of potassium arsenite, as indicated. Nevertheless, the course was not satisfactory, because of the persistent congestive heart failure, which in the last year of life was characterized by paroxysmal dyspnea at night and on exertion.

5. All estimations of the enlargement of the liver or spleen were made by measuring from the lower border of the ribs in the midclavicular line of the side involved.

Electrocardiograms displayed a low T wave, a slurred QRS complex and a shifting pacemaker. Roentgenograms at different times showed first a normal chest with a normal-sized heart, and, later, fine granular infiltration of the pulmonary fields and signs of pulmonary congestion.

In 1935 osteoporosis of the ribs was demonstrated. In December 1935 230 roentgens of radiation was given over the painfully enlarged cervical lymph nodes. This was the first roentgen therapy that was given after the patient came under our care in 1931.

On July 23, 1936, the patient was hospitalized because of severe cardiac asthma, rectal bleeding and profound weakness. At this time he complained of tenderness of the soles. The cardiac symptoms improved rapidly with rest in bed and appropriate medication. The melena was found to be due to a polyp or a leukemic infiltration. This was treated satisfactorily with 780 roentgens of radiation to the perineum. When admitted to the hospital the patient had taken no solution of potassium arsenite for about six weeks, and the leukocyte count was 80,000. After ten days of treatment with this drug in doses of 10 to 21 minims (0.6 to

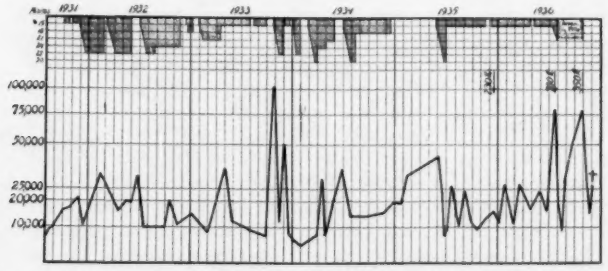


Chart 1 (case 1).—The leukocyte counts and the total daily doses of solution of potassium arsenite in minims.

1.3 cc.) daily, the leukocyte count declined to from 15,000 to 20,000. At this time the dermatologist diagnosed the painful condition of the feet as arsenical hyperkeratosis and advised the use of a less toxic preparation—pills containing arsenic trioxide. The pills prepared in the clinic contain 9 mg. of arsenic trioxide. Two of these were given daily until the patient was discharged. After that he took 4 pills weekly until his final admission to the hospital. When he entered the hospital on July 23, 1936, glycosuria was discovered for the first time, although specimens of urine had been examined frequently in the outpatient department. This amounted to 2 Gm. in the twenty-four hour specimen. The value for blood sugar during fasting was 205 mg. per hundred cubic centimeters. With a diet containing 120 Gm. of carbohydrate, 50 Gm. of protein and 90 Gm. of fat, the glycosuria stopped, and the value for blood sugar decreased to 110 mg. The diet was then increased to 180 Gm. of carbohydrate and later to 230 Gm. of carbohydrate, 65 Gm. of protein and 90 Gm. of fat, with no return of the glycosuria. The patient was discharged on August 5 in fair condition.

He was readmitted for three days on August 18 because of severe paroxysmal dyspnea provoked by the hot weather. When he left the hospital he entered a convalescent home, where no examinations of the blood or urine were made. On November 6 he returned to the hospital because of severe cardiac asthma. The leukocyte count was 33,600, and because of his poor general condition the

patient was given no more arsenic. He received about 350 roentgens of radiation to the inguinal and mediastinal lymph nodes, which brought the leukocyte count down to 13,500. The first twenty-four hour specimen of urine contained 142 Gm. of sugar, and during fasting the value for blood sugar was 259 mg. and that for cholesterol was 165 mg. With a diet of 150 Gm. of carbohydrate, 70 Gm. of protein and 150 Gm. of fat for seven days, the urinary value for sugar declined to 43 Gm. The diet was then changed to 100 Gm. of carbohydrate, 60 Gm. of protein and 150 Gm. of fat. Values of from 12 to 15 Gm. of sugar in the urine persisted, and the blood sugar value during fasting remained at 255 mg. The diet was then increased to 200 Gm. of carbohydrate, 60 Gm. of protein and 100 Gm. of fat, and insulin was given. Surprisingly small amounts of insulin were required: 35, 20, 20, 10, 15, 10, 15 units, respectively, on consecutive days. With this regimen the blood sugar value during fasting changed to 171 mg. and the urinary value for sugar decreased to 2.5 Gm. in twenty-four hours. The patient died rather suddenly of heart failure on December 2, approximately seven years after the onset of leukemia.

Gross Postmortem Examination (by Dr. Paul R. Cannon).—The skin was brown, dry and apparently keratotic over the abdomen. The soles of the feet were unusually thick and scaly, particularly over the heels, and there was a small fleshy wart on the small toe of the left foot. The cervical, axillary and inguinal lymph nodes were moderately enlarged.

The right side of the pleural cavity contained no fluid; the left was obliterated by fibrous adhesions. The left lung was vascular, and the parenchyma was friable in the posterior portion. The right lung was edematous. The bronchi were thick walled and contained no pus. The pericardial cavity contained no fluid. The heart weighed 310 Gm., and the right chambers were distended. The right auricle was filled by a lobular mass of cream-colored blood clot, slightly mottled externally by red but on the cut surfaces pearly throughout. Similar white clots were present in the right ventricle and the pulmonary artery. On the left the myocardium averaged from 15 to 17 mm. in thickness and contained anteriorly a firm fibrous patch, measuring 1.5 by 1 cm. There were small fibrous patches in the form of linear streaks throughout the myocardium. The coronary arteries were calcified, particularly the anterior descending branch on the left. The aorta showed marked atheroma and calcification.

The liver weighed 1,950 Gm. and the capsular surface was somewhat nodular. The organ cut with increased resistance and presented a surface made up of lobules varying from 2 to 10 mm. in diameter. Some were whitish, and all were separated by an increased amount of fibrous tissue. The spleen weighed 515 Gm. and was covered by fibrous adhesions which bound it to the lateral peritoneal wall and to the stomach. The capsule laterally was an opaque tissue 1 cm. thick in places. The organ cut with increased resistance, and its surfaces were of an unusual (almost rocklike) hardness. It consisted mainly of increased fibrous trabeculae, with intervening portions of grayish red tissue. The pancreas was small, firm and fibrous. There was moderate epitheliosis of the esophagus. The gastric mucosa had a distinctly mamillated appearance, the nodules having a diameter of from 2 to 5 mm. There were many submucous hemorrhages in the colon and some erosions. The lower portion of the rectum showed no leukemic nodules or polyps. The kidneys were normal, except for one leukemic mass in the pelvis, measuring 15 by 7 mm.

A portion of the liver was given to the coroner's chemist for analysis. It contained 62.5 mg. of arsenic per hundred grams of tissue.

Histologic Postmortem Examination (by Dr. Cannon).—"The sinusoids and portal areas (of the liver) are diffusely infiltrated with myeloid cells, the majority of which are mature polymorphonuclear leukocytes, although occasional myelocytes may be seen. There are no definite leukemic nodules. Mallory stains for connective tissue show a definite portal cirrhosis in a moderately early stage. The hepatic cells are not fatty and do not contain hemosiderin in unusual amounts. There is considerable regeneration of hepatic cells. The gallbladder is normal. Fatty changes are minimal.

"The capsule and trabeculae of the spleen are greatly thickened and hyalinized, and the trabeculae contain occasional areas of hemosiderin deposit. The malpighian bodies are absent, and the red pulp is scanty and largely infiltrated by leukocytes and myelocytes, with a diffuse increase in fibrous tissue.

"The pancreas contains a great increase in interstitial as well as intralobular connective tissue. Round cells and myeloid elements are present in this connective tissue. Islet tissue is inconspicuous but in places shows a definite increase in connective tissue. The smaller arteries and arterioles are thick walled. There is no hemosiderin.

"The bone marrow shows marked hyperplasia, immature myeloid elements and some absorption of trabeculae. There are occasional areas of fibrous replacement of bone marrow.

"The myocardium shows considerable diffuse and focal myofibrosis, with occasional accumulations of leukemic cells. Lipochrome pigmentation shows only in stains for fat.

"The skin of the sole of the foot shows marked hyperkeratosis, with absence of pigmentation of the stratum germinativum and of inflammation of the corium. The skin of the body shows less marked hyperkeratosis but exhibits hemosiderin-filled macrophages scattered through the corium.

"The plicae of the stomach are prominent, and the mucosa is densely infiltrated by leukemic cells.

"The tracheobronchial and abdominal lymph nodes are hyperplastic and densely infiltrated by leukemic cells.

"The leukemic clot from the heart consists almost entirely of leukemic cells in various stages of maturation and fibrin, with few red corpuscles."

Comment.—This patient's leukemic blood picture was well controlled with solution of potassium arsenite alone for four and a half years. Roentgen irradiation was given to the clavicular region for painfully enlarged lymph nodes, to the perineal region for a rectal polyp or leukemic infiltration, to the inguinal nodes because of tenderness and enlargement and to the mediastinal region because of cough. The spleen, the traditional recipient of roentgen therapy, was given none. Pills containing arsenic trioxide were given in doses calculated to supply as much arsenoxide as the usual dose of solution of potassium arsenite did not keep the leukocyte count down (chart 1), whereas the last roentgen therapy to the inguinal region promptly reduced the count. The terminal diabetic episode was peculiar, and the easy control with a diet rich in carbohydrate and small amounts of insulin is of interest. Joslin's series of diabetic patients includes only one (case 7260) with myeloid leukemia. Hemochromatosis, which is superficially like the con-

dition in the present case, is also accompanied with cirrhosis of the liver, but the patient requires large amounts of insulin. In Joslin's textbook there is nothing to guide one in deciding whether the cirrhosis, the arsenic, the fibrosed pancreas or destiny induced this patient's diabetes. There is no proof that the portal cirrhosis was due to arsenic, but with regard to the high arsenic content of the liver and the general recognition of arsenic as a possible etiologic agent, it seems most likely. At no time during his illness did this patient have herpes zoster or any definite neuritic pain.

Case 2.—The patient, a 56 year old American man, was first seen at the University of Chicago Clinics on Sept. 22, 1933. He complained of fatigue, dyspnea, cough and pain in the left upper portion of the abdomen of two years'

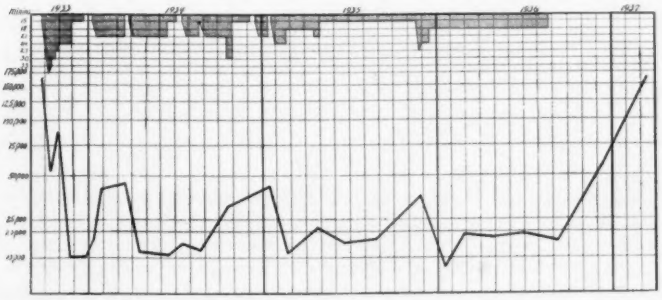


Chart 2 (case 2).—The leukocyte counts and the daily doses of solution of potassium arsenite.

duration and of increasing severity. He was married and had two healthy children. He had always been well and was of moderate habits.

Physical examination revealed moderate enlargement of the lymph nodes generally. The spleen, which was somewhat tender, filled the left iliac region and extended downward to the umbilicus. The Wassermann reaction of the blood was negative, and the urine was normal.

A blood count showed: hemoglobin, 7.8 Gm.; erythrocytes, 2,460,000, and leukocytes, 164,800. The differential count showed: myeloblasts, 11 per cent; promyelocytes, 19 per cent; myelocytes, 3 per cent; metamyelocytes, 1 per cent; polymorphonuclears, 51 per cent; monocytes, 10 per cent; lymphocytes, 4 per cent, and normoblasts, 15 per hundred leukocytes. The stained films of the blood were distinctive because of the many mitotic figures in the erythroblasts and occasionally in the myelocytes.

Course.—Five minims (0.3 cc.) of solution of potassium arsenite three times a day was ordered, the dose to be increased by 1 minim (0.06 cc.) daily until unpleasant symptoms resulted. The data on the leukocyte counts and the doses of arsenic are shown in chart 2. At the onset of treatment and at intervals thereafter iron was given, and the hemoglobin value and red corpuscle count were easily kept at high levels. Three months after treatment with solution of potassium arsenite was started the patient had generalized erythema for one day.

In April 1934, eight months after coming under our care, the patient showed his maximum weight, and one examiner described finding a small amount of free fluid in the abdomen. On his next visit to the clinic the patient said he felt much better, he weighed 2 Kg. less and there was no sign of a fluid wave. After that the only difficulty he encountered was with fairly severe bronchitis in cold damp weather. In spite of this he was able to conduct his business and go hunting, and he felt fairly well. In August 1936 he yielded to a friend's enthusiasm for chiropractic treatments and stopped taking solution of potassium arsenite in September. The leukocyte count in August was 17,000, and the spleen extended 2 or 3 cm. below the left costal margin. The patient returned to the clinic, repentant, with a leukocyte count of 163,000 and with the spleen palpable 9 cm. below the left costal margin. The arsenic therapy was resumed.[5a]

Comment.—From a cytologic point of view this patient's leukemia seemed severe, with many primitive cells and many mitoses; but the course with solution of potassium arsenite has been satisfactory. He took the drug almost continuously until his recent defection. It seems certain that this man had arsenical hepatitis at the time that ascites was detected. No lesions of any sort have appeared on the skin, and it is with great interest that we anticipate continuance of the arsenic regimen.

CASE 3.—The patient, a 30 year old American business man, was referred to the University of Chicago Clinics on Jan. 25, 1930, with the diagnosis of chronic myeloid leukemia. He had had headaches and fatigue during the previous year and pain in the left upper portion of the abdomen of two weeks' duration. He was a widower; his past history and family history were noncontributory.

Physical examination revealed gross enlargement of the spleen, which caused the abdomen to protrude. The viscus was firm and tender and extended to within 2 cm. of the symphysis pubis and just across the midline. The liver was felt 3 cm. below the right costal margin. There was no enlargement of the lymph nodes. The Wassermann reaction of the blood was negative. Examination of the urine did not reveal any abnormality. A blood count showed: hemoglobin, 11 Gm.; erythrocytes, 3,620,000, and leukocytes, 535,000. The differential count showed: myelocytes and metamyelocytes, 44 per cent; polymorphonuclears, 45 per cent; eosinophilic myelocytes and polymorphonuclears, 10 per cent, and normoblasts, 4 per hundred leukocytes. The basal metabolic rate was plus 41 per cent.

Course.—The patient was given a series of nine roentgen treatments in fifteen days over the long bones and the spleen. The total dose was about 1,800 roentgens. After this series the leukocytes numbered 167,000, the basal metabolic rate was plus 10 per cent and the stained film contained fewer myelocytes. On February 8 the leukocyte count was 12,100, and the spleen was palpable only 8 cm. below the left costal margin. The leukocytes numbered 6,200 on April 5. The patient received no treatment of any sort until May 1931, when he was hospitalized again because of a sudden increase in the leukocyte count. He received five roentgen treatments, totaling about 950 roentgens, over the long bones and the thoracic portion of the spine. The leukocyte count (chart 3) decreased from 73,000 to 14,600 after the fifth treatment. In June 1931 solution of potassium arsenite was

5a. In June 1937, after this paper was written, the patient's leukocyte count was 12,900, and he was back at work.

prescribed. It was taken by the patient in twenty-one day cycles, starting with 5 minims (0.3 cc.) three times a day and increasing the dose 1 minim (0.06 cc.) daily until a dose of 9 minims (0.55 cc.) three times a day was reached. After the twenty-first day the treatment was stopped; the patient rested for three weeks and then began all over again. The usual result was a variation of the leukocyte count between about 40,000 and 6,000. In December 1931 herpes zoster developed. and a month later, when the patient was seen at the clinic, he was in excellent condition. The spleen was barely palpable. The blood count showed: hemoglobin, 16.6 Gm.; erythrocytes, 4,790,000, and leukocytes, 63,300. The differential count was: promyelocytes, 2 per cent; myelocytes, 6 per cent; metamyelocytes, 8 per cent; polymorphonuclears, 69 per cent; basophils, 5 per cent; eosinophils, 1 per cent; lymphocytes, 6 per cent, and normoblasts, 0.

The patient continued with the solution of potassium arsenite and was able to keep the leukocyte count almost within normal limits, but resting from the use

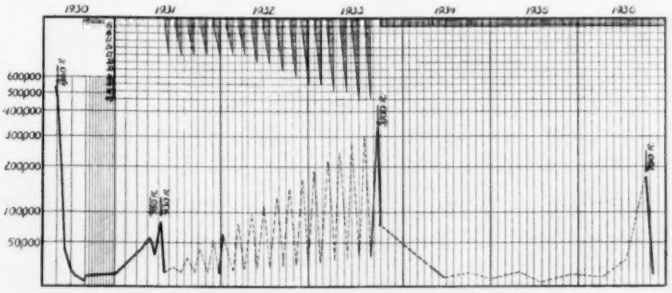


Chart 3 (case 3).—The leukocyte counts and the daily doses of solution of potassium arsenite.

of the drug would be followed by an increase to over 100,000 in three weeks. He returned to the clinic in September 1933 because he felt poorly. He told of having numbness of the legs and an ataxic gait, which improved when the arsenic was stopped. At this time the leukocytes numbered 340,000. He was given another series of roentgen treatments, 3,700 roentgens to the spleen and long bones over a period of eleven days. When he left after this treatment the leukocyte count was 73,000. During the next year he took about 15 minims (0.9 cc.) of solution of potassium arsenite daily, stopping for three weeks whenever the leukocyte count was less than 6,000. He was last seen by us in June 1934, when the leukocyte count was 11,000; the spleen was palpable only on inspiration, and his condition was satisfactory. Contact with this patient has been maintaned by correspondence. In October 1936 the leukocyte count was 180,000, and he received 800 roentgens of radiation at the Harper Hospital in Detroit. On Nov. 10, 1936, the leukocytes numbered 10,200 and the erythrocytes, 4,300,000, and the hemoglobin value was 85 per cent. Since 1934 he has taken solution of potassium arsenite regularly and in general according to the scheme previously mentioned.

Comment.—This case illustrates the possibilities of benefit in thoroughly controlled cases of chronic myeloid leukemia. The man is intelligent and has had a leukocyte count made weekly for years. Throughout the seven year course of the disease he has attended to his business,

traveled and remarried and until recently has been healthy. The only evidence of arsenic intoxication that he has shown, aside from nausea, has been the herpes zoster and the neuritis, which occurred early and disappeared.

CASE 4.—A 45 year old housewife entered the Billings Hospital on April 27, 1931. She complained of severe pain in the left upper portion of the abdomen of one day's duration and easy fatigue and weakness throughout the preceding year. Six months before she came to the clinic she was told that her spleen was enlarged, and she was given a diet and diathermy treatments. Her health had always been good. She had had two children and no miscarriages. The menses were regular and not excessive.

On physical examination there were marked pallor and minor enlargement of all the lymph nodes. The abdomen protruded, and the spleen, which filled the left iliac region and extended 10 cm. below the left costal margin, was tender. Exami-

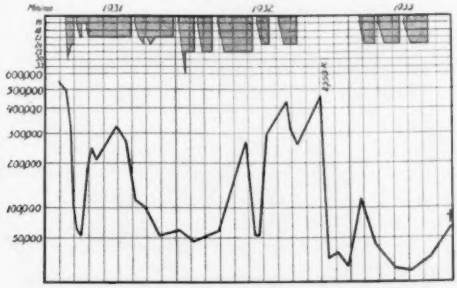


Chart 4 (case 4).—The leukocyte counts and the daily doses of solution of potassium arsenite.

nation of the urine did not reveal any abnormality. The Wassermann reaction of the blood was negative. The blood count showed: hemoglobin, 8.5 Gm.; erythrocytes, 2,600,000, and leukocytes, 570,000. The differential count was: myelocytes, 16 per cent; basophilic myelocytes, 8 per cent; metamyelocytes, 20 per cent; polymorphonuclears, 52 per cent; eosinophils, 3 per cent, and basophils, 1 per cent.

A diagnosis of chronic myeloid leukemia and acute perisplenitis was made. Two days later a friction rub was heard over the spleen, and in the course of ten or twelve days the perisplenitis subsided.

Course.—While this patient was in the hospital, solution of potassium arsenite was given in the usual manner. Chart 4 shows graphically the excellent response to this treatment. For one year her condition was fair, but the white cell count never reached normal levels, and the anemia did not improve strikingly. The spleen decreased somewhat in size, so that the right border receded to the left of the midline. In the summer of 1932 the spleen increased in size, and the leukocyte count steadily rose. The patient tolerated the arsenic poorly, and by August 1932 could take only 21 minims (1.3 cc.) daily without provoking nausea and diarrhea. She suffered intensely from the heat and was hospitalized for a week in August. At that time the hemoglobin value was 9.2 Gm.; the erythrocyte

count, 3,200,000, and the leukocyte count, 368,000. During the next two months she grew steadily worse, and on November 2 she returned to the hospital for roentgen therapy. At this time examination of the blood showed: hemoglobin, 8 Gm.; erythrocytes, 2,800,000, and leukocytes, 450,000. She was given 2,340 roentgens over the spleen in the course of twelve days, and on the day of her discharge, November 16, the leukocytes numbered 22,000. The size of the spleen diminished after this until it extended only to the umbilicus. The patient felt fairly well until June 1933, when she became anemic, weak and feverish. She entered the hospital on July 26. The blood count was: hemoglobin, 4.8 Gm.; erythrocytes, 2,000,000, and leukocytes, 64,000. The spleen was tender and filled the entire left side of the abdomen. The patient became rapidly worse and died on August 3 of bronchopneumonia.

Comment.—At autopsy the spleen weighed 2,900 Gm. and the liver 2,700 Gm. The histologic appearance of the spleen and the bone marrow was typical of myeloid leukemia. This case illustrates the action of solution of potassium arsenite in the more severe type of leukemia. Certainly the initial response was excellent, but one wonders if the patient's inability to tolerate the large doses of arsenic or some inherent difference in the disease accounts for the unsatisfactory course as compared with that of the third patient. Great difficulty was experienced in attempting to keep this patient's hemoglobin value at a safely high level. No complications of the arsenical therapy except gastro-intestinal disturbances occurred.

CASE 5.—A 28 year old housewife of Italian parentage was first seen at the University of Chicago Clinics on Jan. 12, 1931, seeking further treatment of a condition diagnosed elsewhere as lymphatic leukemia. She related that she had been perfectly well until she became pregnant in February 1930. Throughout gestation she suffered continuously from headaches, pain in the back, nausea and vomiting. On November 19, under the care of a midwife, she was delivered precipitously of a normal 6 pound (2,722 Gm.) girl. Delivery was followed by severe postpartum hemorrhage. The physician who was called controlled the hemorrhage and discovered an enlarged spleen. Three weeks later the patient was taken to the Burnside Hospital and given approximately four-tenths of an erythema dose of roentgen therapy. This reduced the leukocyte count from 188,000 to 132,000.

Examination at the clinic showed an enlarged spleen, which extended to the midline from the xiphoid to the umbilicus, filled the left iliac region and extended 16 cm. below the left costal margin. It was firm and smooth but not tender. There was no enlargement of any of the palpable lymph nodes. The Wassermann reaction of the blood was negative. Examination of the urine did not reveal any abnormality. The blood count showed: hemoglobin, 12.5 Gm.; erythrocytes, 3,670,000, and leukocytes, 195,000. The differential count was: myelocytes, 3 per cent; metamyelocytes, 9 per cent; polymorphonuclears, 56 per cent; monocytes, 11 per cent; lymphocytes, 10 per cent; eosinophils, 2 per cent, and basophils, 3 per cent.

The diagnosis was chronic myeloid leukemia.

Course.—When first seen the patient was having considerable intestinal distress, so administration of solution of potassium arsenite was delayed, and only iron

was given to improve the red cell count. The leukocyte count increased to 388,000 in March. From March 26 to April 10 she was given 700 roentgens of radiation over the spleen. As a result the leukocyte count fell to 86,000. When it began to increase in June 1931, solution of potassium arsenite was prescribed. Chart 5 shows graphically the course of the leukocyte counts and the doses of the drug. During the succeeding year the patient was in good health except for troublesome chronic bronchitis during the winter. In June 1932 the soles were sore, and the dermatologists made a diagnosis of arsenical (?) keratosis. At about the same time the patient began to tolerate arsenic less well, and on October 5 she entered the hospital for more irradiation. The examination of the blood showed: hemoglobin, 13 Gm.; erythrocytes, 3,450,000, and leukocytes, 167,000. The differential count was: myeloblasts, 9 per cent; promyelocytes, 4 per cent; myelocytes, 7 per cent; metamyelocytes, 1 per cent; polymorphonuclears, 60 per cent; eosinophils, 2 per cent; basophils, 8 per cent; monocytes, 4 per cent; lymphocytes, 4 per cent, and normoblasts, 8 per hundred leukocytes.

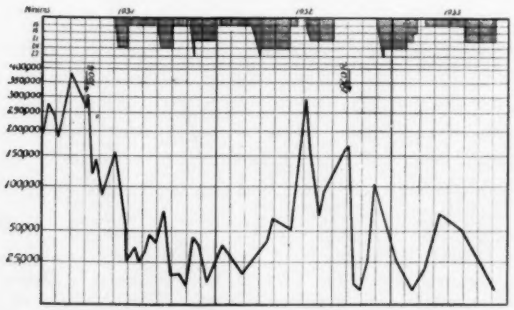


Chart 5 (case 5).—The leukocyte counts and the daily doses of solution of potassium arsenite.

The spleen, which had become decreased in size after the first series of roentgen treatments, almost filled the entire left side of the abdomen, but it was not tender. In eight days the patient was given 1,900 roentgens of radiation over the spleen. When the patient was discharged, on October 14, the leukocytes numbered 15,000. By taking solution of potassium arsenite in small doses almost continuously, the patient kept the count low, but her general condition was poor. She was last seen by us in November 1933 and since then has been under the care of other physicians. The course after she left the clinic is unknown to us.

Comment.—This case is interesting because the patient went through pregnancy and parturition in the early stage of leukemia. The response to therapy with solution of potassium arsenite so soon after a course of roentgen therapy is instructive, since it suggests that arsenic may be given as soon after roentgen therapy as the leukocyte curve ceases to fall. The keratosis which this patient had was mild and appears to have regressed, for after the time the diagnosis was made while her feet were being examined for fungi, there is no further mention of foot trouble.

CASE 6.—A 40 year old Slovakian man came to the University of Chicago Clinics on Oct. 9, 1931. He related that suddenly two years previously he felt severe pain in the left upper portion of the abdomen. He had to remain in bed and consulted many physicians. Finally in the fall of 1929 a diagnosis of myeloid leukemia was made, and he was given thirty-five roentgen treatments. The spleen, which had been "enormous," decreased in size, and the patient was able to return to work. In the summer of 1931 the spleen enlarged again, and the patient received fifteen more roentgen treatments just before registration at the clinic. His past and his family history were irrelevant; he had always been robust until the present illness.

Examination showed roentgen pigmentation of the skin of the abdomen. The spleen protruded and was felt 3 cm. to the right of the midline and 17 cm. below the left costal border. There was no friction rub, and the viscus was firm and not tender. The Wassermann reaction of the blood was negative. Examination of

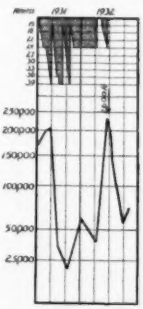


Chart 6 (case 6).—The leukocyte counts and the daily doses of solution of potassium arsenite.

the urine did not reveal any abnormality. The blood count showed: hemoglobin, 11.2 Gm.; erythrocytes, 3,770,000, and leukocytes, 163,200. The differential count was: myeloblasts, 2 per cent; promyelocytes, 2 per cent; myelocytes, 8 per cent; eosinophilic myelocytes, 1 per cent; metamyelocytes, 21 per cent; polymorphonuclears, 55 per cent; eosinophils, 2 per cent; basophils, 4 per cent; monocytes, 1 per cent; lymphocytes, 4 per cent, and normoblasts, 3 per hundred leukocytes.

Course.—The patient was given solution of potassium arsenite in the usual manner but had to consume large amounts before the leukocyte count decreased. Chart 6 gives a graphic representation of the leukocyte counts and the doses of arsenic. The patient was well until January 1932, when herpes zoster developed. In February he complained of breathlessness and weakness and asked for more roentgen therapy. On February 26, after no solution of potassium arsenite had been taken for two weeks, the leukocytes numbered 232,000. From then until March 28 he received 2,650 roentgens of radiation over the spleen and the long bones. At that time the leukocyte count was 64,000. The differential count was: myeloblasts, 5 per cent; promyelocytes, 7 per cent; myelocytes, 1 per cent; eosinophilic myelocytes, 2 per cent; basophilic myelocytes, 2 per cent; metamyelo-

cytes, 6 per cent; polymorphonuclears, 57 per cent; basophils, 8 per cent; lymphocytes, 8 per cent; monocytes, 8 per cent, and normoblasts, 5 per hundred leukocytes.

After this the patient disappeared and could not be traced by our follow-up letters.

Comment.—This is another case in which herpes zoster developed in the course of treatment with solution of potassium arsenite. It is of interest, too, because it illustrates how refractory some patients may be to the drug. But it is to be noted that persistence in increasing the dose produced the desired, if only temporary, result.

COMMENT

The development of arsenical keratosis, arsenical cirrhosis or arsenical neuritis as a consequence of the therapeutic use of arsenic depends on the form of the drug employed, the duration of its administration and a special susceptibility of the patient. The form of arsenic used for our patients is arsenous trioxide, or arsenoxide, a white crystalline powder. Its highly poisonous properties have been known since the Christian era, and as a chief constituent of "aqua Tofana" (a solution containing arsenic) it was well known in the fifteenth and sixteenth centuries. Solid arsenoxide is used therapeutically chiefly in the "Asiatic pill" (7 mg. per dose), but, as was shown in the description of case 1, it is less effective than are solutions. Dry white arsenic is poorly absorbed from the intestinal tract, and the smallest single fatal dose recorded by Witthaus [6] was 2 Gm. Solutions of white arsenic were prepared early, and as "tasteless ague drops" they were a popular medicine in England prior to the general use of quinine for malaria. A Dr. Thomas Fowler, of Stafford, England, developed a preparation of arsenoxide, potassium carbonate and tincture of lavender, which was described in "The Edinburgh New Dispensatory" [7] for 1794. This recipe contained about 1 per cent of arsenous trioxide and is still used with unchanged proportions as liquor arsenicalis B. P., or solution of potassium arsenite U. S. P. (more commonly called Fowler's solution). The preparation is poisonous, and 15 cc. taken in "broken doses in four days" [8] has caused death. This amount is equivalent to 150 mg. of arsenoxide. In therapeutic practice the ordinary dose ranges from 0.6 to 2 cc. per day (9 to 30 minims) in divided doses and represents from 6 to 20 mg.

6. Witthaus, R. A., and Becker, T. C.: Medical Jurisprudence, Forensic Medicine and Toxicology, ed. 2, Baltimore, William Wood & Company, 1911, vol. 4, p. 439.

7. Duncan, A.: The Edinburgh New Dispensatory, ed. 4, Philadelphia, T. Dobson, 1794, p. 102.

8. Peterson, F.; Haines, W. S., and Webster, R. W.: Legal Medicine and Toxicology, ed. 2, Philadelphia, W. B. Saunders Company, 1923, vol. 2, p. 207.

of arsenoxide. Stockman,[9] in a report of a case of arsenical cirrhosis associated with the taking of liquor arsenicalis, stated that when this drug was given to children with chorea in the usual doses, pigmentation of the skin occurred after the administration of 17,900, 9,450, 12,600, 1,050, 360, 3,000, 260, 450, 12,000, 1,950 and 690 mg. of arsenic, respectively. He quoted Gowers as saying that the smallest amount of arsenic which he had ever known to give rise to pronounced arsenical pigmentation was equivalent to about 11,000 minims (7,300 mg. of arsenic) of liquor arsenicalis during two years. Gowers' usual dose was 0.3 cc. three times a day. More recently Halter [10] studied the effect of arsenous trioxide injected intramuscularly daily into patients with dermatologic conditions. He considered a decrease in the leukocyte count to about 4,000 as evidence of intoxication. The drug was given in amounts, increased daily, of from 2 to 10 mg. In thirteen of twenty-six patients with psoriasis so treated leukopenia developed. Seven of these showed other signs of intoxication. When leukopenia occurred, these patients had received 185, 48, 232, 134, 100, 215 and 155 mg. of arsenoxide, respectively. In eight of a group of fifteen patients with other dermatoses leukopenia developed. No patient received more than 280 mg. in a course of treatment; one patient was given three courses, and the leukocyte count reached 4,000, 5,000 and 4,300 after 185, 136 and 280 mg. of arsenic, respectively. The lowest count was seen in a 4 year old child whose leukocytes numbered 2,100 after 135 mg. of arsenoxide had been given. Delépine,[11] who performed experiments on rats as a part of the investigation of the Manchester outbreak of arsenical poisoning in beer drinkers, concluded that a dose "of $\frac{1}{150}$ to $\frac{1}{25}$ grain daily is capable of producing injurious effects in the ill-fed or weak individuals." The beer which was responsible for this epidemic was estimated to contain from 10 to 60 mg. of arsenoxide per gallon, and the victims, mostly heavy drinkers, probably consumed from 5 to 30 mg. of arsenoxide daily.

Toxicologically this marked variation in susceptibility to arsenic intoxication is important, and it is unfortunate that so few competent analyses are reported of the arsenic content of the viscera of persons receiving large amounts therapeutically. Several analyses after acute poisoning have been recorded, but these are of interest chiefly to the criminologist. It is generally accepted that absorbable forms of arsenic are eliminated solely by the kidneys, although small quantities are

9. Stockman, R.: Chronic Arsenic Poisoning, Edinburgh M. J. **27**:1-10, 1921.

10. Halter, K.: Untersuchungen über die Leukocytenzahl bei Darreichung anorganischen Arsens, Klin. Wchnschr. **15**:52-54 (Jan. 11) 1936.

11. Delépine, in Report of the Royal Commission on Arsenical Poisoning, London, His Majesty's Stationery Office, 1903, vol. 1, appendix 16, p. 185.

deposited in the bones, the skin and the hair. Dutcher and Steel [12] gave a dog 35 mg. of arsenic and recovered 71 per cent from the urine in the next twenty days. Scolosuboff [13] fed a dog from 5 to 15 mg. of sodium arsenite daily for thirty-four days. The dog was killed, and the analysis disclosed the following values for arsenic: 0.25 mg. per hundred grams of muscle, 2.71 mg. per hundred grams of liver, 8.85 mg. per hundred grams of brain and 9.33 mg. per hundred grams of spinal cord.

McNally [14] quoted from a thesis of Garnier [15] in which it was reported that in two patients who died of tuberculosis while under treatment with solution of potassium arsenite U. S. P. the brain contained more arsenic than did the liver. In the Royal Commission's investigation [11] of the Manchester epidemic, arsenic was sought in the viscera, i. e., liver, spleen and intestines hashed together, and in one instance there was found "0.011 grain in 13½ ounces." In three other cases in which death had taken place fourteen, thirty-two and fifty-two days, respectively, after beer was no longer taken, arsenic was detected in the viscera but was present in amounts too small to be weighed. In one case, that of a woman who presented marked symptoms of arsenical poisoning during life and who died twenty-three days after ceasing to take beer, no arsenic at all was detected in the viscera tested. It is also stated that arsenic was detected in the urine fifty-nine days after any beer had been consumed. The quantitative elimination of arsenic in the urine during consumption of solution of potassium arsenite is not known. O'Leary, Snell and Bannick [16] studied the excretion of a man who had arsenical cirrhosis and ascites as a consequence of the use of solution of potassium arsenite U. S. P. About 10 mg. of arsenic per liter of urine was found during the period of study. In two cases of arsenic hepatitis (the type of arsenic used was not mentioned, but it was not neoarsphenamine), Young [17] reported an average daily urinary excretion of 5 mg. over about two weeks. In studying a victim of criminal

12. Dutcher, R. A., and Steel, M.: The Elimination and Retention of Arsenic as Determined by the Koch-Norton Method, J. Am. Chem. Soc. **36**:770-773, 1914.

13. Scolosuboff: Localisation dans les tissus d'animaux empoisonnés, Bull. Soc. chim. de Paris **23**:124, 1875.

14. McNally, W. D.: The Retention of Arsenic in the Organs, J. Am. Chem. Soc. **39**:826-828, 1917.

15. Garnier, L.: Expériences sur la recherche toxicologique de l'arsenic, Thèse de Nancy, no. 107, 1880.

16. O'Leary, P.; Snell, A. M., and Bannick, E. G.: Portal Cirrhosis Associated with Chronic Inorganic Arsenical Poisoning, J. A. M. A. **90**:1856-1859 (June 9) 1928.

17. Young, A. G.: Studies of the Action of Sodium Thiosulphate in Metallic Intoxications, J. Lab. & Clin. Med. **13**:622-628, 1927.

poisoning, probably with arsenoxide, Fonzes-Diaçon and his associates [18] recovered 242 mg. of arsenic from the urine excreted in seven days.

The common complications that occur during the therapeutic administration of solution of arsenoxide are three: polyneuritis, keratosis and cirrhosis. These are usually preceded by so-called subtoxic phenomena and are generally accompanied with arsenical pigmentation of the skin. The polyneuritis appears to occur when the drug is given rapidly; and if ordinary care is taken in the instruction of the patient, it should not occur. The neuritic manifestations vary considerably. Paresthesias, radicular pain and ataxia come early. Later, if use of the drug is continued there is extreme weakness, which may progress to complete flaccid paralysis. In cases of acute involvement the neuritis has been so prominent that such diagnoses as Landry's paralysis and poliomyelitis have been made. Withdrawal of the drug is generally followed by complete but slow recovery of function. In Fonzes-Diaçon's patient profound weakness persisted for many months. Herpes zoster is common in patients chronically poisoned with inorganic arsenicals, and it may be the earliest sign of intoxication of the nervous system. The affinity of the drug for the central nervous system has been mentioned previously.

Cirrhosis with attendant ascites and occasionally jaundice is much more insidious. The first example of this complication given in medical writing was probably that of Bang's [19] patient, who had hydrops and ascites and who recovered under a diuretic regimen. In 1895 Hutchinson [20] reported on a patient who had taken potassium arsenite for psoriasis for eight years. There were palmar and plantar keratoses and ascites, with a large tender liver. The patient recovered from the ascites when the arsenic was withdrawn. Hutchinson was apparently the first physician to state that cirrhosis and ascites can be due to arsenic. Geyer,[21] who reported at great length on the cutaneous lesions of the victims of the epidemic of arsenic poisoning due to contaminated water in Reichenstein, in Schlesien, Germany, described several instances of ascites in patients with enlargement and tenderness of the liver. He also mentioned the cutaneous and the fatty hepatic changes in the

18. Fonzes-Diaçon; Grynfeltt, E.; Rimbaud, L., and Cavalié: Sur un triple empoisonnement par l'arsenic, Ann. de méd. lég. **15**:28-52, 1935.

19. Bang, F. L.: De hydrope ex ingesto arsenico observatio, Soc. med. Havn. collect. **1**:307-309, 1774.

20. Hutchinson, J.: Diet and Therapeutics, Arch. Surg., London **6**:389-391, 1895.

21. Geyer, L.: Ueber die chronischen Hautveränderungen beim Arsenicismus und Betrachtungen über die Massenerkrankungen in Reichenstein in Schlesien, Arch. f. Dermat. u. Syph. **43**:221-280, 1898.

patients at autopsy. He described the cirrhosis and in the critical bibliography accompanying the article gave a reference to an experimental study of arsenic intoxication in animals by Ziegler and Obolonsky.[22] They observed portal fibrosis but concluded that it was not typical portal cirrhosis. In the Manchester epidemic of 1900 many of the victims when first examined showed tenderness and enlargement of the liver, with ascites. Since that time there have been many reports of arsenical hepatitis from the ingestion of small amounts of inorganic arsenicals, either therapeutically or accidentally.[23] Arsenic was so generally recognized as a cause of chronic hepatic damage that Rolleston [24] listed it as one of the etiologic agents of portal cirrhosis. The most recent contribution was that of O'Leary, Snell and Bannick,[16] who reported on two patients who had taken solution of potassium arsenite intermittently for several years and who recovered successfully from the ascites that developed.

The first description in the medical literature of the appearance of cutaneous lesions concurrent with the therapeutic use of arsenic was given in 1847 by Thomas Hunt,[25] who described the characteristic arsenic dermatitis. Since that time a variety of cutaneous lesions have been shown to be the result of the ingestion of inorganic arsenicals, and the deposition of arsenic in the skin has been recognized. Commonest are diffuse erythema and macular lesions. Less frequent are melanoderma and pustular lesions. A late result of exposure is the diffuse brownish red pigmentation, seen commonly among employees of chemical plants and others chronically poisoned. Herpes zoster is more properly considered a neurologic complication. In 1868 Erasmus Wilson [26] published a paper describing a certain type of keratosis which was painful at first and which occurred only among patients taking arsenic. J. C. White,[27] in 1885, reported the sequence of psoriasis, keratosis and malignant epithelioma in a physician who had taken solution of potassium arsenite for twenty-two years. White did not attribute

22. Ziegler, E., and Obolonsky, N.: Experimentelle Untersuchungen über die Wirkung des Arseniks und des Phosphors auf die Leber und die Nieren, Beitr. z. path. Anat. u. Physiol. **2**:291-336, 1888.

23. Broadbent, W.: Hodgkin's Disease and Arsenical Poisoning, Brit. M. J. **1**:1140-1141, 1903. Hamburger, L. P.: Arsenical Pigmentation and Keratosis, Bull. Johns Hopkins Hosp. **11**:87-91, 1900. Stockman.[9]

24. Rolleston, H., and McNee, J. W.: Diseaeses of the Liver, Gall-Bladder and Bile-Ducts, ed. 3, New York, The Macmillan Company, 1929, p. 215.

25. Hunt, Thomas: Further Observations on the Administration of Arsenic, Lancet **1**:92, 1847.

26. Wilson, E.: Clinical Memoranda, J. Cutan. Med. **1**:354, 1867-1868.

27. White, J. C.: Psoriasis, Verruca, Epithelioma: A Sequence, Am. J. M. Sc. **89**:163-173, 1885.

the malignant lesion to the therapy, but Jonathan Hutchinson,[28] who saw the patient later, did and subsequently reported on six patients with cancer of the skin who had taken solution of potassium arsenite for from eight to twenty-two years. There was no question in his mind of the validity of the relationship, and he unhesitatingly advised the discontinuance of the drug when keratosis occurred.

The cutaneous, neural and visceral lesions that result from overdoses of arsenoxide are different from the complications encountered when the more complex organic arsenicals are used. Arsphenamines and derivatives of arsanilic acid may cause exfoliative dermatitis but apparently not keratosis. Acute toxic hepatitis and acute yellow atrophy occur, but patients seldom survive long enough or are dosed thoroughly enough to show hepatic fibrosis, except as a reparative phenomenon. Widespread damage to the capillaries, with purpura, is seen, and a rare and often fatal syndrome—aleukia haemorrhagica (Franck)—occurs. There is no counterpart for this among the complications of arsenoxide therapy. However, the routine use of these organic drugs is not associated with leukopenia, and it is generally recognized that organic arsenicals do not benefit leukemic patients. The amount of metallic arsenic which a patient receives daily is about the same with the two types of drug, and Young [17] found that the daily urine of these patients contained about 5 mg. of arsenic shortly after cessation of therapy, a value that compares well with the excretion of arsenic reported by O'Leary and his associates. The reasons for the difference in the activity of the various forms of arsenic have not been elucidated, although Voegtlin [29] noted that arsenoxides depressed the in vitro consumption of oxygen of normal tissues more than did equivalent amounts of arsanilic acid and arsphenamine derivatives.

The effect of arsenoxide on the leukocytes has been known since Cutler and Bradford,[30] in 1878, using the newest methods for making blood counts, gave solution of potassium arsenite to normal persons, anemic patients and to one man with chronic myeloid leukemia. In the patient with myeloid leukemia a striking remission occurred; the leukocyte count dropped from 1,073,000 to 8,700 in ten and a half weeks. The drug was then discontinued for seven weeks, and the leukocyte count increased to 621,000. Five weeks more of arsenic administration returned the count to 84,000. The normal persons showed a slight

28. Hutchinson, J.: On Some Examples of Arsenic-Keratosis of the Skin and Arsenic-Cancer, Tr. Path. Soc. London **39**:352-363, 1887-1888.

29. Voegtlin, C.; Rosenthal, S. M., and Johnson, J. M.: Influence of Arsenicals and Crystalline Glutathione on the Oxygen Consumption of Tissues, Pub. Health Rep. **46**:339-354 (Feb. 13) 1931.

30. Cutler, E. G., and Bradford, E. H.: Action of Iron, Cod-Liver Oil and Arsenic on the Globular Richness of the Blood, Am. J. M. Sc. **75**:74-84, 1878.

decline in the leukocyte count with comparable quantities of the drug. In 1880, however, Delpeuch [31] reported that the administration of arsenic had no effect on the leukocytes. In Osler's text (first edition, 1892) was recorded a remission induced by solution of potassium arsenite in a patient with myeloid leukemia whose leukocyte count decreased from 500,000 to 4,000. Schwaer,[32] in 1908, described a slight diminution in the leukocyte counts of patients with dermatologic and syphilitic disorders who were under treatment with inorganic arsenic compounds. Halter's [10] finding of leukopenia in half of his patients treated with daily injections intramuscularly of arsenoxide has been referred to previously. Most of the studies of the action of arsenic compounds on the blood which have appeared in the twentieth century have been concerned with the effect of these chemicals on the erythrocytes—a subject that is beyond the scope of this paper.

SUMMARY

A study of the case reports presented here demonstrates that complications resulting from the administration of solution of potassium arsenite to patients with myeloid leukemia are not rare when the course is reviewed critically:

In case 1 there was widespread keratosis of the skin, with definite hyperkeratosis of the soles after five years of arsenical therapy. At autopsy a large fleshy wart was observed, and other smaller ones had diminished in size as a result of treatment with salicylic ointment. The high arsenic content of the liver seems to incriminate the medication as the cause of the portal fibrosis observed.

In case 2 erythema developed that lasted for one day after three months of arsenic therapy. Five months later there was fairly good evidence of ascites (due to hepatitis?) which subsided spontaneously.

In case 3 herpes zoster developed after six months of treatment with solution of potassium arsenite. After taking the drug almost continously for two years the patient had transient neuritis of the legs with paresthesia and ataxia.

In case 5 there was tenderness of the soles after one year of treatment, and a diagnosis of arsenical keratosis was made. This condition improved spontaneously, and subsequent developments are not known.

In case 6 herpes zoster developed after three months of intensive arsenic therapy.

Therefore, five of the six patients presented at one time or another in the course of treatment with solution of potassium arsenite seven

31. Delpeuch: De l'action d'arsenic sur le sang, Thèse de Paris, no. 315, 1880.

32. Schwaer, G.: Ueber die Einwirkung therapeutischer Arsendosen auf die Leukozyten beim Menschen, mit besonderer Berücksichtigung der Atoxyl-Wirkung, Arch. f. Dermat. u. Syph. **90**:77-96, 1908.

complications known to result from arsenic. All these patients after taking the drug for longer than five or six months complained of a troublesome chronic cough, and examination of the chest frequently disclosed moist râles. It is not clear whether this was due to the arsenic or the leukemia. The importance of possible complications of this form of therapy in relation to the probable benefits from solution of potassium arsenite in leukemic patients is hard to judge. Certain it is that the disease for which the patients are being treated will ultimately be fatal, but the therapy should not increase their discomfort. Broadbent [23] recognized that the ascites seen so frequently in his time in patients with blood dyscrasia and Hodgkin's disease was often due to solution of potassium arsenite which they were taking. He was often pleased to find this troublesome disorder disappear when the medication was withheld. Therapeutically induced neuritis is just as uncomfortable and inconvenient to the patient as plantar and palmar keratoses or ascites. Since many patients readily tolerate enough arsenic to produce these complications without suffering unduly from the minor, so-called subtoxic symptoms of conjunctival and nasal congestion and gastrointestinal disorders, the therapeutic principle is obvious: A patient should not be permitted to dose himself to his idea of tolerance with solution of potassium arsenite over long periods without medical supervision. Frequent examination of the soles and palms, frequent palpation of the abdomen and caution in proceeding with the drug when herpes zoster or paresthesia occurs are as necessary as a routine leukocyte count. The possibility that ascites is due to the therapy should be remembered, and when it occurs a long rest period, with administration of diuretic drugs, is indicated. If keratosis appears, we do not believe that permanent interdiction of arsenic—as recommended by Hutchinson—is indicated. Rather, the drug should be discontinued until the soreness leaves and then begun again cautiously. If the leukocyte count does not stay at a low level during the rest periods but rises so rapidly that solution of potassium arsenite must be taken almost continuously, roentgen therapy should be given.

The histories of the patients presented here suggest two other points of therapeutic value: Arsenic therapy and roentgen therapy are not antagonistic, and a remission of leukocytosis may be induced with arsenic as soon as the postirradiation decline of the leukocyte count ceases. Also, years of arsenic medication do not render a patient resistant to roentgen therapy. It is encouraging to note that the patient with a high leukocyte count and the patient with severe cytologic findings (case 2) may respond well to a regimen of arsenic alone. The employment of the twenty-one day cycle of increasing doses of solution of potassium arsenite, followed by twenty-one days of rest, seems to be the most

satisfactory method of giving the drug. With control of the course by making frequent leukocyte counts, especially at the onset of treatment, necessary adjustments of the doses are readily made. Finally, in consideration of the prognosis under either form of therapy, it appears that in patients with typical chronic myeloid leukemia the outlook is best when the hemoglobin and erythrocyte counts can be kept at the highest level. Vigorous effort to attain an approach to normality in this respect is highly important.

CONCLUSIONS

The results of treating six patients suffering from chronic myeloid leukemia with solution of potassium arsenite for prolonged periods are presented, and the value of this drug, either as an adjuvant to roentgen therapy or as the sole therapeutic agent, is affirmed.

In five of these patients the following signs of chronic inorganic arsenical intoxication were noted: herpes zoster, keratosis, cirrhosis and polyneuritis.

The differences in the susceptibility of patients to arsenic with respect to the development of serious complications is considered.

Certain therapeutic principles for the management of chronic myeloid leukemia are drawn from a study of this material.

DERMATOLOGIC MANIFESTATIONS OF THE LYMPHOBLASTOMA-LEUKEMIA GROUP

ERVIN EPSTEIN, M.D.
OAKLAND, CALIF.
AND
KATHERINE MacEACHERN, M.D.
LOS ANGELES

The dermatologic manifestations of the diseases of the lymphoblastoma-leukemia group are often typical, despite the fact that it may be impossible to establish the diagnoses by other clinical and hematologic investigations. For this reason the cutaneous lesions occurring in these diseases are worthy of serious and extensive investigation. Involvement of the epidermis, corium or subcutaneous tissue may be the initial manifestation noted by the patient.

Although in numerous excellent articles this subject has already been discussed, most dermatologists have devoted the major portion of their studies to a consideration of the histopathology, etiology and interrelationships of these diseases. The clinical picture of most of these diseases has been carefully described, but there is a scarcity of reports of large series of cases investigated from the standpoint of the cutaneous manifestations. Most authors have tended to group mycosis fungoides, lymphosarcoma, lymphogranulomatosis (Hodgkin's disease) and lymphatic leukemia under the generic term lymphoblastoma. Others have included numerous other conditions, such as Spiegler-Fendt's sarcoid and reticulo-endotheliosis.

These processes are probably etiologically related and certainly offer similar clinical and microscopic characteristics. However, it is unfortunate that the tendency to consider all of them as variants of the same process is gaining favor. Much valuable work has been carried out to establish the identity of the diseases, and this should not be lightly discarded. While an individual patient may show what appear to be different diseases of the same group at different stages of his illness, this is unusual. Lymphosarcoma may temporarily resemble lymphogranulomatosis pathologically, or vice versa, but the histologic criteria on which these diagnoses are based are not inflexible. The fact that any of these conditions may terminate with a leukemoid blood picture is probably not of great significance. Marked lymphocytosis or leuko-

From the Department of Dermatology and Syphilology, the Los Angeles County Hospital.

cytosis with the presence of numerous immature cells may be noted in other conditions besides those of the lymphoblastoma series.

Three types of cutaneous lesions may be observed in patients suffering from diseases comprising the lymphoblastoma-leukemia group. These are the specific lesions, the toxic manifestations ("lymphoblastomids" and "leukemids") and the accidentally associated conditions. These are differentiated by clinical rather than by histopathologic criteria. The petechiae or furuncles of a patient with leukemia may contain

TABLE 1.—*Frequency and Types of Cutaneous Involvement*

Disease	No. of Cases	Cases of Cutaneous Involvement	Cases of Specific Lesions	Cases of Ids	Cases of Associated Lesions
Lymphogranulomatosis	156	83 (53.2%)	12 (7.6%)	51 (32.7%)	4 (2.5%)
Lymphosarcoma	122	29 (23.7%)	17 (13.9%)	23 (18.8%)	3 (2.4%)
Myeloid leukemia	90	43 (47.7%)	5 (5.5%)	47 (52.2%)	2 (2.2%)
Lymphatic leukemia	60	28 (46.6%)	5 (8.3%)	27 (45.0%)	1 (1.6%)
Acute leukemia*	6	3 (50.0%)	0	3 (50.0%)	0
Lymphoblastoma*	5	4 (80.0%)	3 (60.0%)	0	1 (20.0%)
Monocytic leukemia†	4	3 (75.0%)	2 (50.0%)	1 (25.0%)	0
Plasma cell leukemia	1	1 (100.0%)	1 (100.0%)	0	0
Reticulo-endotheliosis	1	0	0	0	0
Totals	445	194 (43.5%)	45 (10.0%)	154 (34.6%)	11 (2.4%)

* More exact classification was impossible with the information at hand.
† Probably a stage of myeloid leukemia.

TABLE 2.—*Types and Frequency of Specific Cutaneous Lesions*

Disease	No. of Cases	Cases of Nodules	Cases of Exfoliative Erythroderma	Cases of Ulcers	Cases of Sinus Formation	Cases of Plaques
Lymphogranulomatosis	12	2 (16.6%)	8 (66.6%)	2 (16.6%)	2 (16.6%)	0
Lymphosarcoma	17	15 (88.2%)	0	2 (11.7%)	0	0
Myeloid leukemia	5	4 (80.0%)	0	0	0	1 (20.0%)
Lymphatic leukemia	5	2 (40.0%)	1 (20.0%)	1 (20.0%)	0	1 (20.0%)
Acute leukemia	0	0	0	0	0	0
Lymphoblastoma	3	1 (33.3%)	2 (66.6%)	0	0	0
Monocytic leukemia	2	2 (100.0%)	0	0	0	0
Plasma cell leukemia	1	0	0	1 (100.0%)	0	0
Reticulo-endotheliosis	0	0	0	0	0	0
Totals	45	26 (57.8%)	11 (24.4%)	6 (13.4%)	2 (4.4%)	2 (4.4%)

leukemic cells and may therefore be considered as specific lesions from the histologic standpoint. However, they are obviously nonspecific clinically and are discussed under the ids. The third group includes psoriasis, senile angiomas, mercury dermatitis and other lesions encountered during this study. These are of no diagnostic importance.

The material forming the basis of this study was taken for the most part from the records of patients in the Los Angeles County Hospital. Table 1 offers the salient facts regarding the incidence of lesions of the skin and mucous membrane among these patients. Mycosis fungoides and Spiegler-Fendt sarcoid were not included, as this inves-

tigation is concerned with the cutaneous manifestations of the diseases that are usually studied by the internist.

LYMPHOBLASTOMA CUTIS AND LEUKAEMIA CUTIS

Specific lesions occurred in 10 per cent of the patients comprising this series. Table 2 offers the statistical findings for this group. Obviously, broad generalizations cannot be drawn from a study of 45 patients, but certain trends that are indicated are of interest.

Lymphogranulomatosis.—The characteristic cutaneous lesion in Hodgkin's disease is the so-called exfoliative erythroderma. This occurred in 66.6 per cent of the patients presenting specific cutaneous lesions. It is characterized by generalized erythema, exfoliation and infiltration. As the disease progresses the skin becomes hyperpigmented and inelastic. As a rule intractable pruritus accompanies this process. In 2 patients the involved lymph nodes became suppurative, and draining sinuses formed. This corresponds to the scrofuloderma of tuberculosis. One elderly woman presented an ulcer which had developed over a necrotic lymph node, while another patient presented a stellate ulceration of the buccal mucous membrane that histologically proved to be Hodgkin's disease. According to Senear and Caro,[1] ulceration may be secondary to necrosis of a cutaneous or subcutaneous nodule, to necrosis of lymph nodes and the overlying skin or to necrosis of large cutaneous tumors. The ulcerative type of lymphogranulomatosis is most likely to be confused with epithelioma, but biopsy can establish a definite diagnosis. Nodules were noted in only 2 patients in this series.

Lymphosarcoma.—Specific cutaneous lesions are most commonly noted in lymphosarcoma (13.9 per cent), while the ids are least often seen (18.8 per cent) in this division of the group. Metastatic nodules constitute the most frequent dermatologic finding. These were noted in 88.2 per cent of the patients in this series with specific lesions. The nodules may be superficial or subcutaneous. They are firm but lack the extreme hardness of metastatic carcinoma. The lesions are usually bright red, although they may have a blue tinge. If the lesion is located deeply, the overlying skin may not be discolored. Occasionally, metastatic nodules may be noted in close proximity to the primarily involved lymph node. In contradistinction to lymphogranulomatosis, exfoliative erythroderma did not occur once among the 122 patients with lymphosarcoma. This, plus the rarity of nodules in Hodgkin's disease, allows the dermatologist to make a clinical differentiation between the two conditions and forms a link in the chain of evidence

1. Senear, F. E., and Caro, M. R.: Ulcerative Hodgkin's Disease of the Skin, Arch. Dermat. & Syph. **35**:114 (Jan.) 1937.

pointing to the individual identity of these two conditions. Ulcers, forming as a result of necrosis of lymph nodes, were the only other specific lesions noted in these cases.

Leukemia.—The cutaneous lesions of myelogenous leukemia are just as distinctive as those of the two first-named conditions. The most characteristic manifestation is the presence of numerous blue to red or skin-colored shotty nodules that are most common on the trunk and upper extremities, although they may be generalized. Mercer [2] stated that in monocytic leukemia the nodules may vary in size and color from day to day. These lesions were noted on 8 of 161 patients with various types of leukemia. Grouping the myeloid and monocytic leukemias together, nodules of this type occurred in 6 of the 7 patients presenting specific lesions. The seventh had a localized infiltrated plaque. The appearance of leukemic nodules in the skin is believed to be of grave prognostic import; [3] Sydenstricker and Phinizy [4] reported an example of monocytic leukemia in which there were purple macules. According to Hollander, Kastlin, Permar and Schmitt,[5] Burckhardt's [6] patient offered the only example of erythroderma occurring in myelosis mentioned in the literature.

In lymphatic leukemia the incidence was fairly well distributed between nodules, ulcers, plaques and exfoliative erythroderma. Loveman [7] stated that the cutaneous manifestations of lymphatic leukemia are more common than those of myeloid leukemia. Studied on a percentage basis, these two groups were about equal (46.6 versus 47.7 per cent), although specific infiltrations were more common in the former (8.3 versus 5.5 per cent). The patient with plasma cell leukemia presented an ulceration with a surrounding infiltrated red areola on the finger. A biopsy established the diagnosis, which was confirmed by examination of the blood smear and bone marrow. One woman with monocytic leukemia had dermatitis venenata after the local application of 3.5 per cent tincture of iodine, and numerous specific nodules soon

2. Mercer, S. T.: The Dermatosis of Monocytic Leukemia, Arch. Dermat. & Syph. **31**:615 (May) 1935.

3. Weil, P. E., and Isch-Wall, P.: A Case of Chronic Myeloid Leukemia with Terminal Development of Cutaneous Tumors, Bull. et mém. Soc. méd. d. hôp. de Paris **47**:84 (Jan. 26) 1931.

4. Sydenstricker, V. P., and Phinizy, T. B.: Acute Monocytic Leukemia, Am. J. M. Sc. **184**:770 (Dec.) 1932.

5. Hollander, L.; Kastlin, G. J.; Permar, H. H., and Schmitt, C. L.: Myeloid Leukemia with Cutaneous Manifestations, Arch. Dermat. & Syph. **29**:821 (June) 1934.

6. Burckhardt, J. L.: Zur Frage der akuten myeloiden Leukämie, Frankfurt. Ztschr. f. Path. **6**:167, 1910-1911.

7. Loveman, A. B.: Monocytic Leukemia Cutis, South. M. J. **29**:357 (April) 1936.

formed in the affected area, converting it into a plaque that histologically exhibited infiltration with leukemic cells.

Unclassified Lymphoblastomas.—While this group included only 5 patients, 3 showed specific cutaneous lesions. The evidence at hand indicates that in 2 the conditions were probably examples of lymphogranulomatosis, while in the third patient the lesions were suggestive of mycosis fungoides. There was only 1 patient in this series with proved reticulo-endotheliosis, and he presented no dermatologic manifestations.

LYMPHOBLASTOMIDS AND LEUKEMIDS

The incidence of ids in this series is shown in table 3; 154 patients (34.6 per cent) of the entire group displayed some type of nonspecific

TABLE 3.—*Types and Frequency of So-Called Ids*

Lesions	Cases of Lymphogranulomatosis	Cases of Lymphosarcoma	Cases of Myeloid Leukemia	Cases of Lymphatic Leukemia	Cases of Acute Leukemia	Cases of Monocytic Leukemia	Total No. of Cases
Cases	156	122	90	60	6	4	
Hemorrhagic lesions	4 (2.5%)	4 (3.2%)	27 (30.0%)	15 (25.0%)	2 (33.3%)	1 (25.0%)	53 (11.9%)
Pigmentation	15 (9.6%)	2 (1.6%)	2 (2.2%)	1 (1.6%)	0	0	20 (4.5%)
Stomatitis	1 (0.6%)	3 (2.4%)	11 (12.2%)	4 (6.6%)	1 (16.6%)	0	20 (4.5%)
Pruritus	12 (7.6%)	4 (3.2%)	0	2 (3.3%)	0	0	18 (4.0%)
Maculopapules	12 (7.6%)	0	3 (3.3%)	1 (1.6%)	0	0	16 (3.6%)
Herpes zoster	4 (2.5%)	1 (0.8%)	1 (1.1%)	1 (1.6%)	0	0	7 (1.5%)
Bullae; vesicles	3 (1.8%)	1 (0.8%)	2 (2.2%)	0	0	0	6 (1.3%)
Herpes simplex	1 (0.6%)	3 (2.4%)	0	0	0	0	4 (0.9%)
Furunculosis	0	1 (0.8%)	2 (2.2%)	1 (1.6%)	0	0	4 (0.9%)
"Eczema"*	2 (1.2%)	0	0	0	0	0	2 (0.4%)
Lichenoid papules	0	1 (0.8%)	0	1 (1.6%)	0	0	2 (0.4%)
"Toxic erythema"*	0	2 (1.6%)	0	0	0	0	2 (0.4%)
Macules*	0	0	0	1 (1.6%)	0	0	1 (0.2%)
Urticaria	1 (0.6%)	0	0	0	0	0	1 (0.2%)
Vaginal ulcers*	0	1 (0.8%)	0	0	0	0	1 (0.2%)

* Not described further.

related eruption. As the question as to which lesions should be included in this category is a matter of opinion, the inclusion of some of them is rightfully open to discussion.

Hemorrhagic Tendencies.—Petechiae and ecchymoses are by far the most common cutaneous lesions seen in leukemia. This is probably due to a decrease in the number of platelets in the circulating blood.

Of the 161 patients with leukemia 27.9 per cent displayed hemorrhagic tendencies, despite the fact that bleeding from the mucous membrane was not included in this tabulation. These lesions were usually noted in acute leukemia or in the terminal stages of the chronic leukemias. In comparison with these figures, dermal or subdermal hemorrhages were seen in only from 2.5 to 3.5 per cent of the patients with Hodgkin's disease or lymphosarcoma. The terminal hematologic picture in these conditions is likely to be that of aplastic anemia. At times vesicles, bullae, macules and papules may be coexistent.

Pigmentation.—Hyperpigmentation is a common finding in lymphogranulomatosis but is comparatively rare in other diseases of the lymphoblastoma-leukemia group. It may be localized or generalized and varies markedly in intensity in different cases. According to Cole,[8] the mucous membranes are usually spared. The pigmentation may be the residual of a former eruption. Treatment in the form of arsenic or irradiation may cause or accentuate this type of lesion. The possibility that the pigmentation is secondary to the pressure of an enlarged lymph node on the sympathetic nervous system or to involvement of the adrenal cortex by lymphoblastomatous tissue also must be considered.

Stomatitis.—Under this heading are included all grades of involvement of the mouth, ranging from simple stomatitis to noma. As in the case of hemorrhagic tendencies, lesions of the oral cavity are at least four times as frequent in leukemias as in the related entities under discussion. The appearance of stomatitis, angina or unusual lesions in the mouth is an indication for a careful hematologic investigation.

Pruritus.—Itching without the presence of visible lesions should lead one to suspect the presence of a member of this group. The pruritus is apt to be severe and intractable. According to Goeckerman and Wilhelm,[9] the itching is characteristically experienced under the skin, but this point did not prove to be of great value in this series. The presence of essential pruritus is more suggestive of Hodgkin's disease than of any of the other conditions considered, although it must be admitted that more common etiologic factors for this distressing symptom are to be found outside the lymphoblastoma-leukemia group. The cause of pruritus in these diseases has not been established. Shelmire [10] said he believed it to be due to the absorption of toxic substances from the altered lymph nodes. Golay [11] and Milian and Blum [12] said they considered it as being secondary to disturbances of the nervous system.

"Toxic Rashes."—In this group are included the erythemas, maculopapular morbilliform eruptions, "eczemas" and other nonspecific entities. Here, too, lymphogranulomatosis leads the list. The mechanism producing these lesions is unknown, and their clinical characteristics run the gamut from macules to papules to wheals to vesicles to bullae to

8. Cole, H. N.: The Cutaneous Manifestations of Hodgkin's Disease: Lymphogranulomatosis, J. A. M. A. **69**:341 (Aug. 4) 1917.

9. Goeckerman, W. H., and Wilhelm, L. F. X.: Lymphoblastoma, California & West. Med. **44**:517 (June) 1936.

10. Shelmire, B.: Hodgkin's Disease of the Skin, South. M. J. **18**:511 (July) 1925.

11. Golay, J.: Sur le rôle du système sympathique dans la pathogénie d'une grand nombre de dermatoses, Ann. de dermat. et syph. **3**:407, 1922.

12. Milian, G., and Blum, P.: Prurigo lymphadenique: Sa nature nerveuse, Bull. Soc. franç. de dermat. et syph. **27**:5, 1920.

furuncles. The furuncles might be placed in a separate group, for they are probably secondary to the lowering of the resistance resulting from the systemic disease. Examples of this group of conditions were noted in 7.6 per cent of the 445 patients comprising this series.

Herpes.—Zoster occurred in 1.5 per cent of the patients. It was most common in lymphogranulomatosis, appearing in 2.5 per cent of the patients. As zona occurs in 1 or 2 per cent of all cases of cutaneous disorders,[13] this is possibly of less significance than is usually considered to be the case. Craver and Haagensen [14] reported 7 instances (2.1 per cent) of herpes zoster among 329 patients with lymphoblastoma, although they noted 7 per cent among patients with lymphosarcoma and 4.5 per cent among those with Hodgkin's disease. Halle [15] found 11 examples of zoster generalisatus among 16 patients with lymphatic leukemia. In the leukemias the lesions tend to be hemorrhagic. The associated lymphoblastoma probably serves as a contributing factor to this virus infection. Lockwood, Johnson and Narr [16] reported a case in which herpes zoster was the initial manifestation of a lymphogranulomatous involvement of a vertebra. The appearance of zona should serve as an indication for a roentgenographic investigation of the nearest vertebrae. Herpes simplex was seen in only 0.9 per cent of the patients, a figure that does not serve as an argument for the relationship of herpes simplex and this group of diseases.

Other Conditions.—Jaundice and subcutaneous edema are common manifestations. However, they are not included in this series, as they are seldom considered from the dermatologic standpoint.

COMMENT

The frequency of cutaneous lesions in diseases of this group has varied in different series. The usually accepted figure for Hodgkin's disease is that of Ziegler,[17] who noted cutaneous manifestations in 25 per cent of his patients. He found further that in from 5 to 12 per cent of the patients cutaneous eruptions constituted the presenting sign or symptom. Both Cole [8] and Miller [18] reported that 40 per cent of their patients with lymphogranulomatosis presented cutaneous lesions.

13. Corson, E. F., and Knowles, F. C.: Unusual Cases of Herpes Zoster, Arch. Dermat. & Syph. **5**:619 (May) 1922.

14. Craver, L. F., and Haagensen, C. D.: Note on Occurrence of Herpes Zoster in Hodgkin's Disease, Lymphosarcoma, and the Leukemias, Am. J. Cancer **16**:502 (May) 1932.

15. Halle, H.: Zoster and Leukemia, Arch. f. Dermat. u. Syph. **159**:238, 1930.

16. Lockwood, I. H.; Johnson, E. T., and Narr, F. C.: Hodgkin's Disease with Bone and Skeletal Involvement, Radiology **14**:445 (May) 1930.

17. Ziegler, K.: Die Hodgkinsche Krankheit, Jena, Gustav Fischer, 1911.

18. Miller, H. E.: Lymphogranulomatosis Cutis, Arch. Dermat. & Syph. **17**: 156 (Feb.) 1928.

Miller found only 2 patients with specific infiltrations among 55 patients. Barron [19] noted dermal complications in only 16 per cent of his 24 patients with Hodgkin's disease. While the incidence of cutaneous lesions is higher in lymphogranulomatosis in our series (53.2 per cent), the average for the entire group (43.5 per cent) agrees with the statistics of Cole and Miller. Our greater number of specific lesions may be accounted for partly by remembering that we included exfoliative erythrodermas in this group.

The question of the specificity of lesions may also be discussed, and it is here that the histologic versus the clinical point of view must be stressed. Previously we indicated that the finding of a specific infiltrate on the microscopic slide does not establish a lesion as being clinically specific. The examples of the petechiae and the furuncles were mentioned. Conversely, the lack of specific cells in histopathologic studies does not disprove the specificity on clinical grounds. In reviewing the literature, it was noted that some authors have considered exfoliative erythroderma as a specific lesion while others have claimed that it is a toxic manifestation of the lymphoblastomatous or leukemic process. Some have stated that the eruption may be nonspecific, even though cells typical of leukemia may be demonstrated at biopsy. Montgomery, in a discussion of Barney's [20] paper, reported the finding of lymphoblastomatous cells in the grossly normal skin of patients with diseases belonging to this group. If so-called specific infiltrates can be found in normal skin, one must question the wisdom of classifying lesions as specific or nonspecific on histologic evidence alone.

Clinically a nondescript eczematous lesion may evolve into a manifestation indistinguishable from postarsenical exfoliative dermatitis and then into typical erythroderma. We have seen this occur and feel that the various lesions merely represent different phases of the same process. In our patient histologic examination revealed a mild inflammatory infiltrate in the upper portion of the corium, with the development of spongiosis early and of a lymphoblastomatous infiltrate later. Miller [18] reported the occurrence of specific nodules in a patient with clinically typical pityriasis rubra of Hebra. We have seen a blood picture resembling that of lymphatic leukemia develop in a patient with a similar condition.

In reviewing the tables showing the incidence of the exfoliative dermatitis-malignant erythroderma complex in lymphogranulomatosis, one is impressed by its frequent occurrence as well as by its rarity in lymphosarcoma and myeloid leukemia. It is more frequent in lymphatic

19. Barron, M.: Unique Features of Hodgkin's Disease, Arch. Path. **2**:659 (Nov.) 1926.

20. Barney, R. E.: Leukemic Myelosis Associated with Specific Nodules in the Skin, Arch. Dermat. & Syph. **27**:725 (May) 1933.

leukemia than in the splenomyelogenous form. Our study leads to the belief that this complex is of differential diagnostic importance and should be considered as a specific manifestation of this group of diseases, despite the fact that similar eruptions may be seen in conditions unrelated to this group.

It is impossible for a study of this type definitely to establish the pathogenic identity of this group of diseases. Admittedly, the dermatologic aspects may vary and seemingly change from one condition to another, even as do the pathologic and hematologic characteristics. We can only point out that the cutaneous manifestations are often of distinguishing value if present. As stated previously, we believe that these diseases are separate entities.

It is interesting to note that a high percentage of our patients exhibited an obvious focus of infection. However, the results of tampering with the focal infection were in most instances disastrous. This is particularly true in leukemia. In 11 patients in this series dental extraction either precipitated or aggravated the condition. Elimination of foci was ineffectual in every instance in which it was attempted.

Study of this series reiterates the frequency of cutaneous complications among patients afflicted with conditions belonging to the lymphoblastoma-leukemia group. The frequency of so-called specific lesions was found to be much higher than is generally considered to be the case. In these cases careful dermatologic examination coupled with judicious resort to histopathologic study may save the patient the inconvenience and expense of a detailed laboratory and clinical investigation as well as the need for biopsy of a lymph node.

SUMMARY AND CONCLUSIONS

The results of a study of 445 patients suffering from conditions belonging to the lymphoblastoma-leukemia series is presented.

The specific cutaneous lesions are described and their differentiating characteristics noted. Briefly, Hodgkin's disease shows the exfoliative erythroderma complex, the metastatic nodules of lymphosarcoma and the shotty nodules of the face and upper extremity of myeloid leukemia.

The common ids are also discussed, and an attempt is made to explain their pathogenesis.

The importance of herpes zoster as an id is questioned.

An attempt is made to establish the specificity of the exfoliative dermatitis-malignant erythroderma complex.

The importance of dermatologic study in this group of diseases is stressed.

1624 Franklin Street.

1200 North State Street.

METABOLISM OF SODIUM *d*-LACTATE

I. UTILIZATION OF INTRAVENOUSLY INJECTED SODIUM *d*-LACTATE BY NORMAL PERSONS

LOUIS J. SOFFER, M.D.

D. ALFRED DANTES, M.D.

ROBERT NEWBURGER, M.D.

AND

HARRY SOBOTKA, PH.D.

NEW YORK

The object of these experiments was to study the utilization of sodium *d*-lactate by human beings both under normal conditions and in the presence of certain pathologic processes. *D*-lactic acid represents an intermediary stage in carbohydrate metabolism in the cycle involving striated muscle and liver. The confusion which has arisen concerning the conversion of lactic acid into glycogen is in part due to the failure to realize the difference in the nature of the utilization of the *d* and *l* forms. Thus, Meyerhof and Lohmann [1] pointed out that isolated hepatic tissue of the rat was able to synthesize carbohydrate from *d*-lactic acid but hardly from *l*-lactic acid. Cori and Cori [2] have pointed out that if 95 mg. per hundred grams of body weight of *d*-lactic acid per hour is injected into rats, there occurs no appreciable increase in the lactic acid content of either the blood or the urine, while if the experiments are repeated with sodium *dl*-lactate, a considerable urinary excretion of lactic acid occurs. These authors found that from 40 to 95 per cent of the sodium *d*-lactate given orally or injected subcutaneously is retained as glycogen in the liver and none is excreted in the urine. In contrast to this they found that 30 per cent of the *l*-lactic acid is excreted in the urine and hardly any glycogen is formed in the liver. Himwich, Koskoff and Nahum,[3] working with decerebrate dogs, found that the main site of formation of lactic acid was the muscle, while

Aided by a grant from Merck & Co., Inc.

From the Medical Service of Dr. George Baehr and the Division of Laboratories, Mount Sinai Hospital.

1. Meyerhof, O., and Lohmann, K.: Ueber den Unterschied von d- und l-Milchsäure für Atmung und Kohlehydratsynthese im Organismus, Biochem. Ztschr. **171**:421, 1926.

2. Cori, C. F., and Cori, G. T.: Glycogen Formation in the Liver from *d*- and *l*-Lactic Acid, J. Biol. Chem. **81**:389, 1929.

3. Himwich, H. E.; Koskoff, Y. D., and Nahum, L. H.: Changes in Lactic Acid and Glucose in the Blood on Passage Through Organs, Proc. Soc. Exper. Biol. & Med. **25**:347, 1928.

the liver was chiefly concerned with its removal from the blood stream and probably with converting it into glycogen. This is highly probable, since Cori and Cori [4] found that injections of epinephrine, which cause a disappearance of glycogen from the muscle in normal rats, lead to the formation of glycogen from lactic acid in the liver. Elias and Schubert [5] and Janssen and Jost [6] showed that the intravenous injection of sodium *d*-lactate and sodium *dl*-lactate into the intact dog produced no increase in muscle glycogen. They assumed, therefore, that the lactic acid thus introduced was converted into glycogen by the liver. Abramson, Eggleton and Eggleton,[7] working with racemic sodium lactate, found that in the intact anesthetized dog neither the muscles nor the liver synthesizes glycogen or dextrose from this salt. They further found that from 7 to 40 per cent of the injected racemic salt is excreted unchanged in the urine, the concentration of urinary lactate depending on the rapidity of the administration and the amount of the sodium *dl*-lactate injected. In their experiments the carbon dioxide content of the blood was increased, the elevation persisting for several hours after the urinary excretion of lactate was completed. Hartmann and Senn[8] studied the metabolism of sodium *dl*-lactate in children. They injected from 4 to 7 cc. of a molar solution per kilogram of body weight intravenously. The sugar and carbon dioxide contents of the blood rose considerably, and about 18 per cent of the injected lactate was excreted as such in the urine, the remainder being completely utilized within two hours. Most of the injected lactic acid disappeared from the blood stream within one hour. Since the racemic salt is a mixture of both the *d* and the *l* form, they concluded that 80 per cent of the *d*-lactic acid is converted into glycogen while all the *l*-lactate is oxidized.

It seems from the brief summary presented that there is a distinct difference between the behavior of the *d* and that of the *l* form of lactic acid, most of the *d* form being converted into glycogen by the liver, while the *l* form is partially excreted in the urine and the remain-

4. Cori, C. F., and Cori, G. T.: Mechanism of Epinephrine Action: Influence of Epinephrine on Carbohydrate Metabolism of Fasting Rats, with Note on New Formation of Carbohydrates, J. Biol. Chem. **79**:309, 1928.

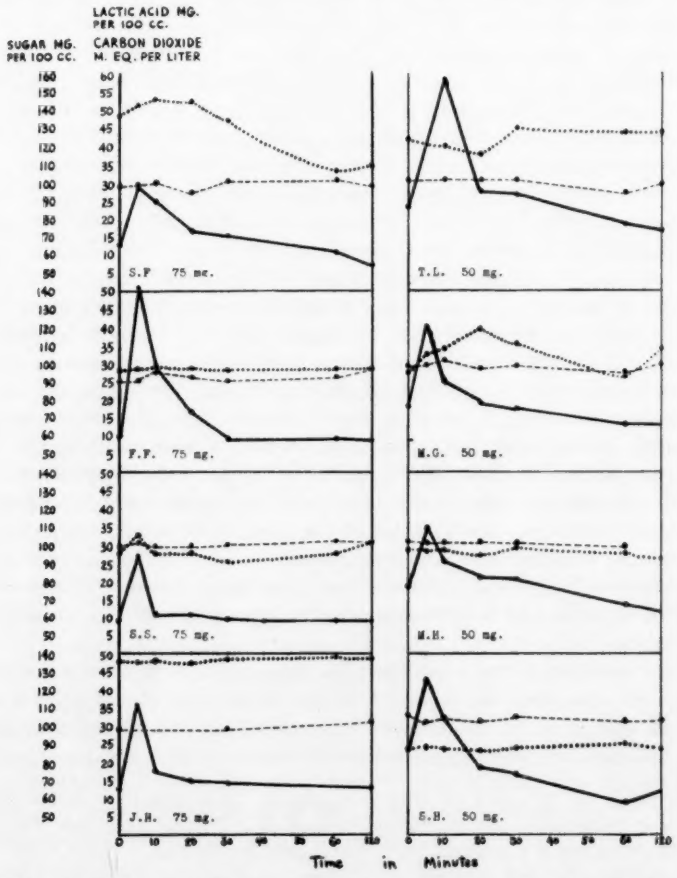
5. Elias, H., and Schubert, E.: Ueber die Rolle der Säure im Kohlenhydratstoffwechsel: III. Säure und Muskelglykogen, Biochem. Ztschr. **90**:229, 1918.

6. Janssen, S. and Jost, H.: Ueber den Wiederaufbau des Kohlenhydrates im Warmblütermuskel, Ztschr. f. physiol. Chem. **148**:41, 1925.

7. Abramson, H. A.; Eggleton, M. Grace, and Eggleton, P.: The Utilization of Intravenous Sodium *r*-Lactate: III. Glycogen Synthesis by the Liver; Blood Sugar; Oxygen Consumption, J. Biol. Chem. **75**:745, 753 and 763, 1927.

8. Hartmann, A. F., and Senn, M. J. E.: Studies in the Metabolism of Sodium-*r*-Lactate: I. Response of Normal Human Subjects to the Intravenous Injection of Sodium *r*-Lactate, J. Clin. Investigation **11**:327, 1932.

der is oxidized and apparently slightly, if at all, utilizable as a carbohydrate intermediary. As a corollary of this it follows that the proportion of the racemic salt which is converted into glycogen is essentially dependent on the amount of *d* salt present in the mixture.



Determinations on the blood. The solid line indicates the values for lactic acid; the dash line, those for carbon dioxide, and the dotted line, those for sugar.

METHOD

In the present series of experiments sodium *d*-lactate was used exclusively. The quantities injected were 50 and 75 mg. per kilogram of body weight in a 14 per cent solution. This concentrated solution was employed in order to eliminate the prolonged time necessary for the injection of more dilute solutions. The persons on whom these studies were conducted were patients convalescing from

uncomplicated appendectomy or herniotomy. All the subjects selected were ostensibly normal except for the operative procedure. In each case at least from five to eight days was permitted to elapse after the operation before the experiments were started. The subject was kept in bed for twenty-four hours before the injection of sodium lactate and during the experiment. He was permitted no food for at least twelve hours before the experiment. A twenty-four hour specimen of urine was collected under toluene as a control, and the total quantity of urine voided during the two hour period of the experiment was used to determine the change in excretion of lactic acid following the injection of sodium *d*-lactate. All samples of blood were collected anaerobically under oil for the determination of the carbon dioxide content, while determinations of the lactic content were made on blood collected in sodium fluoride to prevent clotting and glycolysis. A control sample of blood was drawn, and with the needle in situ the solution of sodium *d*-lactate was then injected. The duration of the injection never exceeded two minutes. Samples of blood were collected five, ten, twenty, thirty, sixty and one hundred and twenty minutes after the injection. No undue reactions were observed in any of the patients.

All analyses were made in duplicate. Determinations of the lactic acid content of the blood and urine were made by the method of Friedemann and his colleagues [9] and the carbon dioxide content of the blood by the method of Van Slyke and Neill.[10]

RESULTS

Lactic Acid in the Blood.—After the injection of sodium *d*-lactate the increase in the lactic acid content of the blood above the control value varied from 15.6 to 41.2 mg. per hundred cubic centimeters, the peak being reached at the end of five minutes. It seemed to make no material difference in the normal person whether 50 or 75 mg. per kilogram of body weight of the test substance was used. After the peak the lactic acid content of the blood fell rapidly, the major drop occurring within twenty minutes, and more gradually thereafter, returning approximately to the control level within thirty minutes. In six of the eight subjects the lactic acid content fell below the control level. This occurred within from one-half to one hour after the injection.

Carbon Dioxide Content of the Serum.—No appreciable change occurred in the carbon dioxide content in any of the experiments.

Blood Sugar.—In only one instance did there occur a significant increase in the values for blood sugar after the injection. This occurred in patient M. G., who received 50 mg. of sodium *d*-lactate per kilogram of body weight. In the remaining instances the values for blood sugar remained remarkably constant.

---

9. Friedemann, T. E.; Cotonio, M., and Shaffer, P. A.: Determination of Lactic Acid, J. Biol. Chem. **73**:335, 1927. Friedemann, T. E., and Kendall, A. I.: Determination of Lactic Acid, ibid. **82**:23, 1929.

10. Van Slyke, D. D., and Neill, J. M.: Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

Results of Injections of Sodium d-Lactate

	Control	Minutes 5	10	20	30	60	120
J. H.; male aged 14; 75 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	12.8	35.8	17.9	14.9	14.2	.....	12.8
Blood sugar, mg. per 100 cc.	135.0	135.0	136.0	134.0	137.0	138.0	137.0
Carbon dioxide content, milliequivalents per liter	29.0	.....	.....	.....	29.0	.....	31.0
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			16.8				
Urine voided during test (2 hr.)			11.3				
S. S.; male aged 24; 75 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	9.1	26.6	10.8	10.6	9.6	8.9	8.9
Blood sugar, mg. per 100 cc.	95.0	105.0	95.0	95.0	90.0	95.0	100.0
Carbon dioxide content, milliequivalents per liter	29.6	30.3	29.9	29.6	30.0	31.0	30.4
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			31.7				
Urine voided during test (2 hr.)			23.5				
F. F.; male aged 7; 75 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	10.0	51.2	29.7	16.3	8.9	9.6	8.9
Blood sugar, mg. per 100 cc.	96.0	97.0	97.0	97.0	96.0	97.0	96.0
Carbon dioxide content, milliequivalents per liter	25.6	25.7	28.4	26.2	25.3	26.4	28.6
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			14.0				
Urine voided during test (2 hr.)			12.9				
S. F.; male aged 20; 75 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	12.6	28.2	24.4	16.3	15.6	10.4	7.4
Blood sugar, mg. per 100 cc.	137.0	143.0	146.0	145.0	134.0	107.0	109.0
Carbon dioxide content, milliequivalents per liter	29.8	29.8	30.0	27.7	30.2	30.5	29.3
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			9.3				
Urine voided during test (2 hr.)			9.3				
T. L.; male aged 14; 50 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	23.4	.....	58.4	27.9	26.6	18.1	16.6
Blood sugar, mg. per 100 cc.	124.0	.....	120.0	116.0	130.0	128.0	128.0
Carbon dioxide content, milliequivalents per liter	30.3	.....	30.5	30.5	30.5	27.6	29.7
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			7.4				
Urine voided during test (2 hr.)			5.8				
M. G.; male aged 22; 50 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	18.0	40.0	25.2	18.9	17.8	13.6	13.6
Blood sugar, mg. per 100 cc.	95.0	105.0	108.0	119.0	111.0	94.0	107.0
Carbon dioxide content, milliequivalents per liter	28.8	29.0	30.7	28.3	29.3	27.9	29.5
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			11.9				
Urine voided during test (2 hr.)			13.0				
M. H.; male aged 24; 50 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	18.1	34.2	25.2	20.7	20.2	13.4	11.3
Blood sugar, mg. per 100 cc.	97.0	96.0	97.0	94.0	98.0	95.0	92.0
Carbon dioxide content, milliequivalents per liter	30.6	30.2	30.3	30.6	30.1	29.8	....
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			12.3				
Urine voided during test (2 hr.)			18.6				
S. H.; male aged 42; 50 mg. per kilogram							
Blood lactic acid, mg. per 100 cc.	23.9	42.3	32.0	18.4	16.6	9.1	11.6
Blood sugar, mg. per 100 cc.	87.0	89.0	87.0	86.0	88.0	90.0	88.0
Carbon dioxide content, milliequivalents per liter	32.8	31.2	....	31.4	32.3	31.7	31.7
Lactic acid, mg. per 100 cc.							
Control 24 hr. urine			13.6				
Urine voided during test (2 hr.)			12.3				

Lactic Acid in the Urine.—In seven of the eight subjects there occurred no increase in the excretion of lactic acid in the urine after the injection of this substance intravenously. In one instance (M. H., who was given 50 mg. per kilogram of body weight) the urinary excretion of lactic acid increased from 12.3 to 18.6 mg. per hundred cubic centimeters.

CONCLUSIONS

Sodium *d*-lactate when injected intravenously into the normal subject disappears rapidly from the blood stream. That it is completely utilized is evidenced by the fact that there occurs no increase in the excretion of this substance in the urine, despite the fact that in most instances the renal threshold for lactic acid is exceeded.[11] On the basis of the available data cited, it seems to be definitely established that the disappearance of the injected sodium *d*-lactate is dependent on its removal from the blood stream by the liver and its conversion into glycogen. This is further substantiated by the data to be presented in a subsequent paper dealing with the utilization of this substance in the presence of hepatic damage.

SUMMARY

The intravenous injection of sodium *d*-lactate in doses of from 50 to 75 mg. per kilogram of body weight is followed by a considerable rise in the concentration of lactic acid in the blood, which attains its peak at the end of five minutes and returns to the control level within one-half hour.

In six of the eight subjects the lactic acid content of the blood fell below the control level within from one-half to one hour after the injection.

In only one of the eight subjects did there occur an increase in the excretion of lactic acid in the urine after the administration of the sodium *d*-lactate.

No appreciable change in the carbon dioxide content of the serum occurred in any of the experiments.

In only one subject did there occur a significant rise in the blood sugar content after the injection of sodium *d*-lactate.

Mr. Roger Steinhardt rendered technical assistance in the experiments.

11. Hewlett, A. W.; Barnett, G. D., and Lewis, J. K.: Effect of Breathing Oxygen-Enriched Air During Exercise upon Pulmonary Ventilation and upon Lactic Acid Content of Blood and Urine, J. Clin. Investigation **3**:317, 1926.

METABOLISM OF SODIUM *d*-LACTATE

II. UTILIZATION OF INTRAVENOUSLY INJECTED SODIUM *d*-LACTATE BY PATIENTS WITH ACUTE DIFFUSE PARENCHYMAL INJURY OF THE LIVER

LOUIS J. SOFFER, M.D.

D. ALFRED DANTES, M.D.

ROBERT NEWBURGER, M.D.

AND

HARRY SOBOTKA, PH.D.

NEW YORK

The metabolism of racemic sodium lactate in the presence of disease of the liver has been studied by Schumacher [1] and Hartmann and Senn.[2] The two optically active enantiomer components constituting racemic lactate differ from each other, according to Cori and Cori,[3] with regard to the manner of their biologic utilization. The *l* form when injected or ingested cannot be converted into glycogen or any intermediate carbohydrate, but its greater portion reappears in the urine, whereas the remainder may be accounted for by the formation of accessory carbon dioxide. On the other hand, *d*-lactate is converted into glycogen by the liver.[4] Hartmann and Senn concluded that the degree of glycogen formation from racemic lactate depends on the proportion of the *d* form present in the mixture.

It seems, therefore, of importance to study the fate of the optically active components separately, especially that of the *d*-lactate, in normal and pathologic human metabolism. In a previous paper we [4a] demon-

Aided by a grant from the Committee on Scientific Research of the American Medical Association.

From the Medical Service of Dr. George Baehr and the Laboratories of the Mount Sinai Hospital.

1. Schumacher, H.: Das Verhalten der Blutmilchsäure bei Leberkranken, Klin. Wchnschr. **37**:1733 (Sept. 9) 1928.

2. Hartmann, A. F., and Senn, M. J. E.: Studies in the Metabolism of Sodium *r*-Lactate: III. Response of Human Subjects with Liver Damage, Disturbed Water and Mineral Balance, and Renal Insufficiency to the Intravenous Injection of Sodium *r*-Lactate, J. Clin. Investigation **11**:345, 1932.

3. Cori, C. F., and Cori, G. T.: The Mechanism of Epinephrine Action: I. The Influence of Epinephrine on the Carbohydrate Metabolism of Fasting Rats, with a Note on New Formation of Carbohydrate, J. Biol. Chem. **79**:309, 1928.

4. (*a*) Soffer, L. J.; Dantes, D. A.; Newburger, R., and Sobotka, H.: Metabolism of Sodium *d*-Lactate: I. Utilization of Intravenously Injected Sodium *d*-Lactate by Normal Persons, Arch. Int. Med., this issue, p. 876. (*b*) Cori and Cori.[3]

strated that sodium *d*-lactate injected intravenously into normal subjects in doses of 75 mg. per kilogram of body weight disappears rapidly from the blood stream. The major drop in the lactic acid level of the blood occurs within twenty minutes, and within one-half hour it returns to its control level. In most instances the lactic acid content fell below the control value within one hour. The disappearance of the injected *d*-lactate is due essentially to its conversion into glycogen by the liver. There occurred no change in the carbon dioxide content of the serum, and in only one instance was there an increase in the urinary secretion of lactic acid.

In the present paper we are reporting the data obtained after the intravenous injection of sodium *d*-lactate into patients with diffuse hepatic disease. Only patients with clinically well defined acute diffuse damage to the hepatic parenchyma were employed. There has been no attempt at present to make a quantitative correlation between the clearance of lactic acid from the blood stream and the clinical severity of the hepatic disease.

PROCEDURE

Of the eight patients studied, three had catarrhal jaundice, four had arsphenamine icterus and one had cirrhosis of the liver with superimposed necrosis. Seventy-five milligrams per kilogram of body weight of sodium *d*-lactate in a 14 per cent solution was injected intravenously. The patients were all confined to bed for at least twenty-four hours before the injection and during the course of the experiment. No food was permitted for at least twelve hours before the performance of the test. A twenty-four hour specimen of urine was collected under toluene as a control, and the total urine voided during the two hour period of the experiment was used to determine the change in excretion of lactic acid following the injection of sodium *d*-lactate. All samples of blood were collected anaerobically under oil for the determination of the carbon dioxide content, while analyses of the lactic acid content were made on blood collected in sodium fluoride to prevent clotting and glycolysis. A control sample of blood was drawn, and while the needle was in situ the solution of sodium *d*-lactate was injected. Samples of blood were collected five, ten, twenty, thirty, sixty and one hundred and twenty minutes after the injection. No undue reactions were observed in any of the patients studied. All analyses were made in duplicate. Determinations of the lactic acid content of the blood and urine were made by the method of Friedemann and his associates,[5] and the carbon dioxide content of the blood was determined by the method of Van Slyke and Neill.[6]

RESULTS

Lactic Acid Content of the Blood.—After the injection of sodium *d*-lactate the increase in the lactic acid content of the blood above the

5. Friedemann, T. E.; Cotonio, M., and Shaffer, P. A.: The Determination of Lactic Acid, J. Biol. Chem. **73**:335, 1927. Friedemann, T. E., and Kendall, A. I.: The Determination of Lactic Acid, ibid. **82**:23, 1929.

6. Van Slyke, D. D., and Neill, J. M.: The Determination of Gases in Blood and Other Solutions by Vacuum Extraction and Manometric Measurement, J. Biol. Chem. **61**:523, 1924.

control level varied from 13.6 to 39.4 mg. per hundred cubic centimeters, the peak being reached at the end of five minutes. The disappearance of the injected lactate from the blood stream occurred slowly; thus, at the end of sixty minutes the lactic acid level was still

Results of Injections of Sodium d-Lactate

	Control	5 Min.	10 Min.	20 Min.	30 Min.	60 Min.	120 Min.
F. D., Laennec's Cirrhosis with Acute Hepatitis							
Blood: Lactic acid, mg. per 100 cc..	20.7	34.3	32.9	....	31.5	23.9	24.7
Sugar, mg. per 100 cc.....	88.0	92.0	87.0	....	90.0	93.0	88.0
Carbon dioxide, m.-eq. per liter....	26.6	26.6	27.0	....	23.9	27.9	26.5
Urine: Lactic acid, mg. per 100 cc...	33.7	....	....	....	....	....	30.1
J. S., Catarrhal Icterus							
Blood: Lactic acid, mg. per 100 cc..	20.5	38.6	35.9	30.9	29.9	28.2	23.6
Sugar, mg. per 100 cc.....	136.0	131.0	134.0	135.0	134.0	131.0	137.0
Carbon dioxide, m.-eq. per liter....	25.8	25.8	26.2	27.5	27.3	25.8	27.3
Urine: Lactic acid, mg. per 100 cc...	15.5	....	....	....	....	....	16.6
A. P., Catarrhal Icterus							
Blood: Lactic acid, mg. per 100 cc..	15.2	54.6	37.9	39.8	25.1	24.1	15.4
Sugar, mg. per 100 cc.....	80.0	82.0	79.0	80.0	80.0	84.0	86.0
Carbon dioxide, m.-eq. per liter....	29.7	29.0	30.0	29.4	28.9	28.9	31.5
Urine: Lactic acid, mg. per 100 cc...	17.7	....	....	....	....	....	17.8
M. R., Arsphenamine Hepatitis							
Blood: Lactic acid, mg. per 100 cc..	16.9	33.8	31.8	30.0	21.9	21.9	21.4
Sugar, mg. per 100 cc.....	110.0	115.0	114.0	107.0	101.0	119.0	115.0
Carbon dioxide, m.-eq. per liter....	29.7	29.7	30.6	29.7	29.7	27.1	31.3
Urine: Lactic acid, mg. per 100 cc...	13.2	....	....	....	....	....	25.5
J. R., Arsphenamine Hepatitis							
Blood: Lactic acid, mg. per 100 cc..	17.4	40.7	35.5	27.6	27.0	18.4	14.8
Sugar, mg. per 100 cc.....	117.0	112.0	....	105.0	110.0	101.0	100.0
Carbon dioxide, m.-eq. per liter....	29.0	....	....	28.0	27.0	28.0	....
Urine: Lactic acid, mg. per 100 cc...	12.0	....	....	....	....	....	21.3
J. Br., Arsphenamine Hepatitis							
Blood: Lactic acid, mg. per 100 cc..	13.3	44.1	29.9	27.1	21.1	20.1	15.0
Sugar, mg. per 100 cc.....	86.0	83.0	83.0	83.0	83.0	83.0	82.0
Carbon dioxide, m.-eq. per liter....	32.4	27.4	24.4	....	27.6	27.0	29.2
Urine: Lactic acid, mg. per 100 cc...	22.9	....	....	....	....	....	34.2
J. Ba., Arsphenamine Hepatitis							
Blood: Lactic acid, mg. per 100 cc..	15.9	45.5	45.3	....	42.0	21.3	16.6
Sugar, mg. per 100 cc.....	100.0	97.0	90.0	....	86.0	85.0	85.0
Carbon dioxide, m.-eq. per liter....	29.9	24.7	25.9	....	25.9	26.4	27.5
Urine: Lactic acid, mg. per 100 cc...	18.7	....	....	....	....	....	20.6
E. L., Catarrhal Icterus							
Blood: Lactic acid, mg. per 100 cc..	11.8	30.3	23.1	25.8	24.0	23.4	20.6
Sugar, mg. per 100 cc.....	94.0	95.0	93.0	92.0	96.0	104.0	103.0
Carbon dioxide, m.-eq. per liter....	26.1	25.2	25.4	25.5	26.0	22.8	22.4
Urine: Lactic acid, mg. per 100 cc...	35.8	....	....	....	....	....	9.4

considerably elevated, and in five of the eight instances it had failed to return to its normal level at the end of two hours.

Carbon Dioxide Content of the Serum.—There was no appreciable increase in the carbon dioxide content of the serum after the injection of lactate in any of the experiments.

Blood Sugar.—There occurred no significant increase in the blood sugar level over the control level in any instance.

Lactic Acid in the Urine.—In five of the eight instances no increase in the excretion of lactic acid in the urine occurred after the injection of the salt intravenously. In the remaining three cases the increase in the urinary excretion of lactic acid varied from 50 to 93 per cent.

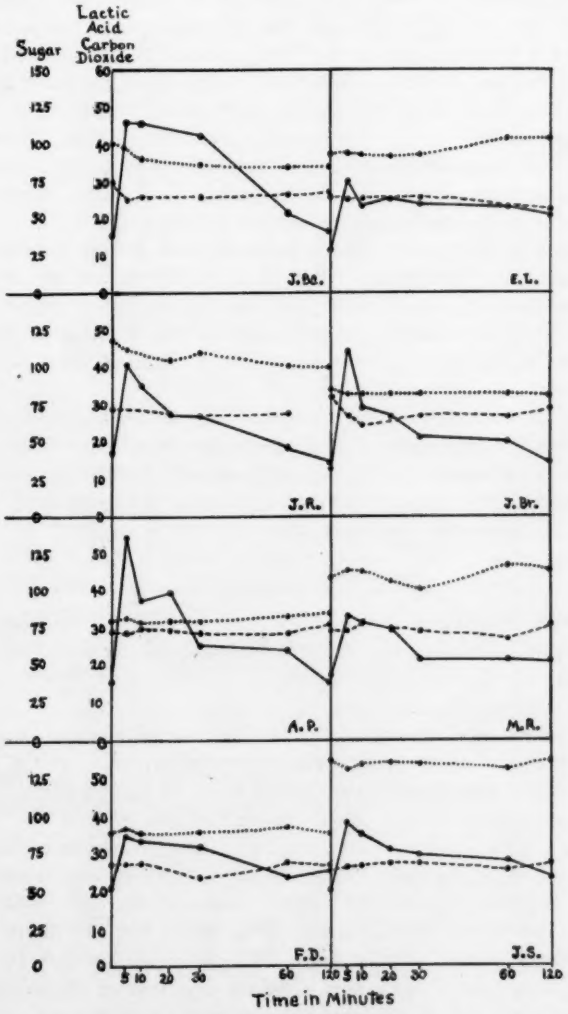


Chart showing the results of injections of sodium *d*-lactate. The solid line indicates the milligrams of lactic acid per hundred cubic centimeters of blood; the dash line, the carbon dioxide content of the blood in milliequivalents per liter, and the dotted line, the milligrams of sugar per hundred cubic centimeters of blood.

CONCLUSIONS

In normal persons the disappearance of intravenously injected sodium *d*-lactate occurred rather rapidly,[4a] so that in all instances the lactic acid content of the blood returned to its approximate control level within one-half hour and fell below the control value within one hour. In the patients with hepatic damage presented in this series there occurred a definite delay in the disappearance of the injected lactate. Thus, at the end of thirty minutes the elevation of the lactic acid content of the blood above the control value varied from 30 to 164 per cent, while at the end of one hour it varied from 15 to 100 per cent. In only one case did the lactic acid content return to its control level within one hour. This occurred in patient J. R., who received only two thirds of the usual dose of sodium *d*-lactate.

In five of the eight instances the lactic acid content had still failed to return to its normal level at the end of two hours, the degree of retention varying from 13 to 74 per cent. In one patient there occurred a drop below the control level at the end of the two hour period. This occurred in the patient who received the reduced dose of sodium *d*-lactate.

One may conclude from these data that in the presence of acute diffuse hepatic parenchymal injury there occurs a definite delay in the utilization of intravenously injected sodium *d*-lactate. This delay is presumably due to the difficulty of conversion by the injured liver of the available *d*-lactate into glycogen.

SUMMARY

Sodium *d*-lactate in doses of 75 mg. per kilogram of body weight was injected intravenously in eight instances of acute diffuse hepatic parenchymal damage, and its rate of disappearance from the blood stream was investigated.

The lactic acid content of the blood remained elevated in all cases at the end of thirty minutes. The degree of retention of the injected lactate above the control value varied from 30 to 164 per cent, while at the end of one hour it varied from 15 to 100 per cent. In only one instance did the lactic acid level return to its approximate control value at the end of this period. This occurred in a patient who received only 50 mg. per kilogram of body weight. In five of the eight instances the lactic acid level was still considerably elevated after two hours.

In three of the eight patients there occurred an increase in the urinary excretion of lactic acid after the injection of the lactate.

No change occurred in either the carbon dioxide or the sugar content of the blood.

Progress in Internal Medicine

SYPHILIS

A REVIEW OF THE RECENT LITERATURE

PAUL PADGET, M.D.
AND
JOSEPH EARLE MOORE, M.D.
BALTIMORE

This review covers publications which appeared during the last six months of 1936 and the first half of 1937. As before,[1] we have found it necessary to exercise a rigid selection of material and largely to exclude the literature on experimental syphilis and on serologic studies.

HISTORY OF SYPHILIS

As a part of the educational feature of the program for the control of venereal disease which is being developed, Winslow [2] and Moore[3] present popular articles in which they briefly review the history of syphilis. Both emphasize that the means for the control of syphilis have been developed and need only to be applied. Moore and Manning [4] studied the records of the Massachusetts Historical Society and discovered that many early settlements in New England were founded largely to secure sassafras for the London markets. It was in demand there as a remedy of many virtues, but chiefly for the treatment of syphilis. Zimmermann [5] reproduces the first treatise on syphilis written

From the Syphilis Division of the Medical Clinic, the Johns Hopkins Hospital and University.

1. (*a*) Moore, J. E.: Syphilis: A Review of the Recent Literature, Arch. Int. Med. **56**:1015 (Nov.) 1935. (*b*) Padget, Paul, and Moore, J. E.: Syphilis: A Review of the Recent Literature, ibid. **58**:901 (Nov.) 1936.

2. Winslow, C. E. A.: The Drama of Syphilis, J. Social Hyg. **23**:57 (Feb.) 1937.

3. Moore, J. E.: The Modern Background of Syphilis Control, Hygeia **15**: 50 (Jan.) 1937.

4. Moore, Merrill, and Manning, Charles: Syphilis and Sassafras: Information Relating to the "Plant of the Sovereign Vertue for the French Pox" and Early Voyages to New England, Am. J. Syph., Gonor. & Ven. Dis. **20**:646 (Nov.) 1936.

5. Zimmermann, E. L.: An Early English Manuscript on Syphilis: A Fragmentary Translation from the Second Edition of Gaspar Torrella's "Tractatus cum consiliis contra pudendagram seu morbum gallicum," Bull. Inst. Hist. Med. **5**:461 (May) 1937.

in English and identifies it as a fragmentary translation from one of the consilia by Gaspar Torrella, of Toledo. Goodall [6] points out that the fame of Fracastor should rest on more than his invention of the word syphilis. The treatise entitled "De contagionibus et contagiosis morbis et eorum curatione," says this author, entitles Fracastor to an important place in the history of epidemiology, because he there described theories both of the intimate nature of contagion and of the living nature of the cause of infection.

Wakefield, Dellinger and Camp,[7] in a study of the skeletal remains of the mound builders of eastern Arkansas, discovered lesions of the long bones, clavicles, skulls and bones of the nose which were similar to the changes produced by syphilis. In one skeleton they found these changes in both tibias, radii and ulnas, one fibula and the bones of the skull. They point out that this multiplicity of lesions is strongly in favor of syphilis as the cause, but they emphasize that the diagnosis of syphilis made solely by study of skeletal remains is always open to question, because there is no way to prove that the changes observed were not the result of some other chronic inflammatory process. Taking the long view, however, they conclude that whereas there is not enough evidence to say with certainty that precolonial Americans had syphilis, the probability is strong that they did. The authors are insistent, however, in avoiding the controversy regarding the New or the Old World origin of the disease.

SPIROCHAETA PALLIDA

Cultivation.—Efforts to grow Spirochaeta pallida in pure culture continue, with an occasional enthusiastic preliminary communication, such as that of Schereschewsky.[8] This author reports that he is able to maintain for many days the viability of S. pallida obtained from the spleens of infected white mice. There is presented, however, no evidence that multiplication occurs. Welfrez [9] is most enthusiastic, although her published results are even less convincing than those of Schereschewsky.

---

6. Goodall, E. W.: Fracastor as an Epidemiologist, Proc. Roy. Soc. Med. **30**:341 (Feb.) 1937.

7. Wakefield, E. G.; Dellinger, Samuel C., and Camp, John D.: A Study of the Osseous Remains of the Mound Builders of Eastern Arkansas, Am. J. M. Sc. **193**:488 (April) 1937.

8. Schereschewsky, J.: Culture de spirochètes pâles provenant de la rate de la souris blanche, Bull. Soc. franç. de dermat. et syph. **43**:1063 (June) 1936.

9. Welferz, Galina: Biologie du spirochète pâle; simple méthode d'obtention du spirochète pâle dans une culture pure et les caractères morphologiques des spirochètes dans les cultures, Bull. Soc. franç. de dermat. et syph. **43**:1065 (June) 1936.

Morphology.—Bessemans and his colleagues [10] undertook to determine the reasons for the lack of agreement between the numbers of spirochetes to be found in material from a rabbit syphiloma by dark field study, on search of smears stained by the Fontana-Tribondeau method and on examination of sections stained by the Dieterlé method. In a large series of comparative studies they observed no characteristic differences between the results obtained by the three methods. They conclude, therefore, that the contradictions are apparent and not real.

In spite of this demonstration of the variability of the results obtained by any of the methods of rendering the spirochete visible, Bessemans [11] describes a method he has devised for counting spirochetes in a homogenized emulsion and experiments which are based thereon. These observations seem to indicate that chancres must contain many more demonstrable spirochetes than lymph nodes in order to be infectious. He postulates therefore that while S. pallida is morphologically a unit, it is functionally variable. This ingenious hypothesis is advanced not only as an explanation of certain anomalies to be observed in the course of the disease in animals experimentally infected with syphilis [12] but also as a counter in the long controversy with Levaditi,[13] who explains similar phenomena by assuming the existence of an invisible form of the spirochete.

Tilden,[14] by appropriate filtration experiments, demonstrated that S. pallida will pass through collodion membranes the pores of which have

10. Bessemans, A.; Janssens, P.; Van Thielen, E., and de Wilde, H.: Affinités tinctoriales et argentiques du tréponème pâle, Bull. Soc. franç. de dermat. et syph. **43**:1073 (June) 1936.

11. Bessemans, A.: Sur la variabilité fonctionnelle de "Treponema pallidum," Bull. Soc. franç. de dermat. et syph. **43**:1084 (June) 1936.

12. Bessemans, A.: La pathogénie de la syphilis inapparente chez le lapin, Bull. Soc. franç. de dermat. et syph. **43**:1111 (June) 1936. Bessemans, A., and de Moor, A.: Ueber das Auftreten der Spirochaeta pallida (Treponema pallidum) im Gehirn und anderer Organen der mit asymptomatischer Lues infizierten Maus, Dermat. Ztschr. **75**:57 (March) 1937.

13. Levaditi, C.; Vaisman, A.; Schoen, R., and Manin, Y.: Recherches expérimentales sur la syphilis (deuxiéme mémoire): Variations de l'activité pathogène et cycle évolutif du virus syphilitique, Ann. Inst. Pasteur **56**:251 (March) 1936. Levaditi, C.; Vaisman, A., and Schoen, R.: Recherches expérimentales sur la syphilis: Étude pathogénique de la neurosyphilis, ibid. **56**:481 (May) 1936. Levaditi, C.; Vaisman, A.; Schoen, R., and Manin, Y.: Sort de "treponema pallidum" sous l'influence thérapeutique de l'arsenic et du bismuth; sa persistance dans les tissus des animaux réfractaires, Bull. Soc. franç. de dermat. et syph. **42**:1813 (Dec.) 1935. Levaditi, C.; Schoen, R., and Vaisman, A.: Étude expérimentale de la neurosyphilis: Influence des souches tréponémiques, Compt. rend. Soc. de biol. **122**:732, 1936.

14. Tilden, Evelyn B.: Filtration of Treponema Pallidum and Treponema Novyi Through Collodion Membranes, J. Bact. **33**:307 (March) 1937.

an average diameter of 0.4 micron. Turner [15] reports the maintenance of viability of spirochetes in rabbit chancres frozen at —78 C. for from four to six months. This is an important step forward in the study of experimental syphilis.

Dissemination.—Raiziss and Severac [16] point out that the rapidity with which S. pallida invades the blood stream after syphilitic infection has occurred is of considerable theoretical interest and of great practical importance in connection with the possibility of transmitting syphilis by blood transfusion. By means of a set of carefully conducted experiments they demonstrated that the organism enters the blood stream of the rabbit immediately after intratesticular inoculation. They conclude from these observations that the greatest care must be exercised to prevent the transmission of syphilis by the transfusion of blood from a donor who has been recently infected. It must be emphasized, however, that the forced distention of tissues and the consequent destruction of natural barriers to dissemination of the virus which occur during experimental inoculation are not analogous to the mode of infection in human beings. The results of these experiments are therefore not applicable to man.

The wide distribution of spirochetes in patients with early syphilis is shown by Frankl.[17] This author obtained serum for dark field examination from areas of apparently normal skin, either by cantharides blister or by sterile abrasion. Spirochetes were regularly present in the material from patients early in the course of syphilitic infection. Charpy [18] presents an interesting report of a student who, fearing that he had been infected with syphilis, insisted on dark field examination of material from the area in which a minor abrasion had been sustained during coitus, two weeks before. The lesion had healed, but material expressed after scarification of the area contained many spirochetes. No organisms were seen in material expressed from other scarified areas of the genital mucosa.

---

15. Turner, T. B.: The Preservation of Virulent Treponema Pallidum and Treponema Pertenue in the Frozen State, J. Clin. Investigation **15**:470 (July) 1936.

16. Raiziss, George W., and Severac, Marie: Rapidity with Which Spirochaeta Pallida Invades the Blood Stream, Arch. Dermat. & Syph. **35**:1101 (June) 1937.

17. Frankl, J.: Le tréponeme dans la peau intacte des individus syphilitiques, Rev. franç. de dermat. et de vénéréol. **12**:196 (April) 1936.

18. Charpy, J.: Constatations de "Treponema pallidum" sous la muqueuse génitale pendant la période d'incubation du chancre, Bull. Soc. franç. de dermat. et syph. **43**:32 (Jan.) 1936.

IMMUNITY IN SYPHILIS

The literature dealing with the multitudinous problems of immunity in syphilis is much too voluminous to be reviewed here in extenso. However, some experimental observations are important enough to require mention. By means of bilateral scrotal inoculation of syphilitic material into rabbits which at varying intervals previously had had a similar inoculation on one side, Gastinel and his co-workers [19] produced further evidence for the development of local immunity early in the course of syphilitic infection. Tani and his collaborators [20] continued their efforts to demonstrate specific antibodies in the serum of men and of animals suffering from syphilis in various stages. From their most recent observations they feel convinced that antibodies always are present but are in much higher titer early in the course of the disease. Beck,[21] however, was unable to demonstrate an increase in the spirocheticidal properties of human blood serum or cerebrospinal fluid after treatment with induced malaria, and in a later communication he [22] presents results entirely contrary to those of Tani and his co-workers.

Jahnel [23] makes an interesting contribution, which would be more valuable if full protocols were provided. In attempts to infect a wide variety of animals with syphilis he fell on certain hibernating rodents, notably the *Siebenschläfer* (rellmouse), which derives its name from its custom of sleeping approximately seven months a year. This animal apparently will spontaneously recover from infection with syphilis during hibernation, but in warm weather the disease persists.

From the clinical standpoint current information and the necessary deductions therefrom are well summarized by Chesney. [24]

> Immunity or resistance to syphilis develops in man as a result of syphilitic infection. The development is gradual and never proceeds so far as that of most of the other immune reactions of human beings. The resistance is not absolute but is only partially effective, and the extent to which it develops varies in different patients. It does not appear to be a function of the humors of the

19. Gastinel, P.; Pulvénis R., and Collart, P.: Recherches sur l'immunité régionale, Bull. Soc. franç. de dermat. et syph. **43**:1141 (June) 1936.

20. Tani, R., and Ôgiuti, K.: Das Wesen der Syphilisimmunität: II. Die spirochätozide Fähigkeit des Syphilisserums, Jap. J. Exper. Med. **14**:457 (Oct. 20) 1936. Tani, T., and Aikawa, S.: Das Wesen der Syphilisimmunität: III. Parabioseversuche mit Kaninchen, ibid. **14**:465 (Oct. 20) 1936.

21. Beck, A.: Investigations on the Problem of Immunity Against Spirochaeta Pallida in General Paralytics Treated with Malaria, J. Ment. Sc. **82**:254 (May) 1936.

22. Beck, A.: The Occurrence of Protective Antibodies in Syphilis, J. Path. & Bact. **44**:399 (March) 1937.

23. Jahnel, F.: Les processus de guérison naturelle dans syphilis expérimentale, Bull. Soc. franç. de dermat. et syph. **43**:1149 (June) 1936; Further Studies in Experimental Syphilis: The Efficacy of Natural Curative Factors, Am. J. Syph., Gonor. & Ven. Dis. **21**:18 (Jan.) 1937.

24. Chesney, Alan M.: Syphilis as a Problem in Immunity, South. M. J. **29**: 1230 (Dec.) 1936.

body, and its development can be prevented by appropriate treatment. Once established, however, it is not immediately dissipated by antisyphilitic agents, if at all. While little is known of its mechanism, it is nevertheless a factor of great importance to the individual concerned. The very fact that the development of this resistance may be interfered with by active treatment in the early stages of the disease places a heavy responsibility upon the physician who undertakes to treat patients with early syphilis. He should clearly recognize that in instituting antisyphilitic therapy he is presuming to interfere with one of nature's own mechanisms, and he should realize that he is not justified in this interfering unless he can improve upon nature. He cannot improve upon nature unless he is prepared and willing to carry out energetic and persistent treatment in the attempt to eliminate the infection from his patient altogether. This is the one lesson which the study of immunity in syphilis makes clear. The conscientious physician will take heed of it.

SEROLOGY

Parran and others [25] present the second report of the Committee on Evaluation of Serodiagnostic Tests for Syphilis:

> In it is described a project in which the directors of thirty state, municipal and private laboratories undertook fifty-one performances of nineteen separate serodiagnostic methods. Eight of these methods were those described by serologists who had participated in the first study to evaluate original tests. For each of these eight methods a control examination was performed by the serologist who originally described the test . . . The specimens submitted in the second project are not, of course, entirely comparable. Because of the difficulties encountered in collecting comparable samples for all participants, it was found necessary to establish four separate groups of serologists. The serologists in each group received comparable samples from the same series of donors. Since different donors were used in each series, comparison cannot be drawn between the percentages of sensitivity and specificity for the methods that were evaluated.
>
> Careful study of the tables which are presented in the second report shows that in some of the state and local laboratories the performance of serologic tests does not compare favorably with the results achieved in the laboratories of the originators of the methods. In some of the former laboratories, false positive reports were made in from 3 to 9 per cent of specimens from nonsyphilitic persons. In others the sensitivity of the tests dropped to an alarmingly low percentage.
>
> The results achieved in other state and local laboratories, however, are quite comparable to those obtained with the control performances.[26]

The variation in the apparent reliability of different laboratories inspired even further comment: [27]

> Every clinician who uses the serologic tests for syphilis should assure himself that (*a*) the laboratory employed is under the direction of a competently trained

25. Parran, T., and others: Efficiency of State and Local Laboratories in the Performance of Serodiagnostic Tests for Syphilis, Am. J. Clin. Path. **7**:20 (Jan.) 1937; Am. J. Pub. Health **27**:15 (Jan.) 1937; Ven. Dis. Inform. **18**:4 (Jan.) 1937.

26. The Efficiency of Serodiagnostic Tests for Syphilis, editorial, J. A. M. A. **108**:728 (Feb. 27) 1937.

27. The Clinician and the Serologic Test for Syphilis, editorial, J. A. M. A. **109**:134 (July 10) 1937.

serologist; that (*b*) intralaboratory check of the accuracy of the test in common use is constantly maintained by the performance of another test of approximately equal specificity and sensitivity; e. g., a complement fixation test is checked by a flocculation test or vice versa, or a flocculation test checked by a different flocculation test; that (*c*) interlaboratory checks of the accuracy of the tests employed are periodically carried out by the exchange of specimens with a different laboratory, and that, (*d*) most important of all, the accuracy of the laboratory is constantly checked against the known clinical diagnoses of the patient from whom specimens are submitted. This implies a close association with a large syphilis clinic.

Hazen [28] acts as spokesman for the committee on evaluation of serologic tests of the cerebrospinal fluid for syphilis. Kline [29] reworks the material of the previous serologic conference and suggests a standard scheme for the interpretation of results of these conferences. Webb [30] reiterates the value of employing two or more tests in the serodiagnosis of syphilis. Taussig and Orgel [31] and Ester [32] provide further evidence that malaria may cause a false positive reaction to occur with an otherwise reliable serologic test for syphilis. Chargin and Rosenthal [33] note that the behavior of the serologic reaction sometimes gives little or no indication of the true course of events in patients with latent syphilis.

OTHER LABORATORY PROCEDURES

Blood.—Varga [34] studied the blood picture in a total of 80 patients in various stages of syphilitic infection. Some of them had received treatment, but most had not. Nothing characteristic of the disease was discovered in the blood picture. The white corpuscles were normal or slightly decreased in number, and there was a tendency toward mild anemia of the hyperchromic type. Coruzzi [35] concludes that the sedi-

28. Hazen, H. H.; Parran, T.; Sanford, A. H.; Senear, F. E.; Simpson, W. M., and Vonderlehr, R. A.: The Evaluation of Serodiagnostic Tests for Syphilis upon the Spinal Fluid, South. M. J. **30**:465 (May) 1937.

29. Kline, B. S.: Evaluation of Results of Flocculation Tests for Syphilis in the Recent American Conference, Am. J. Clin. Path. **7**:139 (March) 1937.

30. Webb, E. L.: The Practical Value of Employing More than One Laboratory Procedure in the Serodiagnosis of Syphilis, J. Lab. & Clin. Med. **22**:184 (Nov.) 1936.

31. Taussig, E., and Orgel, M. N.: The Kahn Test in Malaria, J. Lab. & Clin. Med. **22**:614 (March) 1937.

32. Ester, F.: Sul comportamento di alcune sieroreazioni della sifilide sul siero di sangue dei non luetici inoculati sperimentalmente con malaria terzana benigna, Gior. di batteriol. e immunol. **17**:502 (Oct.) 1936.

33. Chargin, L., and Rosenthal, T.: Paradoxical Behavior of Wassermann Test in Latent Syphilis, J. A. M. A. **107**:1374 (Oct. 24) 1936.

34. Varga, A.: Die Bewertung des Blutbildes bei Syphilis, Arch. f. Dermat. u. Syph. **175**:214 (Feb. 5) 1937.

35. Coruzzi, C.: Sulla velocità di sedimentazione delle emazie nella lue e nel campo dermatovenereologico, Gior. di clin. med. **16**:1540 (Dec. 30) 1935.

mentation rate for patients with syphilis is so variable that the method is of no value in differential diagnosis.

Cerebrospinal Fluid.—Stary, Kral and Winternitz,[36] from a chemical study of the Pandy test, conclude that the test is not specific for globulin but that it precipitates all the proteins of the cerebrospinal fluid. They agree with others, however, on its clinical usefulness. Deadman, Elliott and Smith [37] advocate the use of colloidal carbon (Carter's black india ink no. 358) to replace other colloidal preparations in testing the cerebrospinal fluid. On the basis of the literature and his own experience in 1,301 cases Donati [38] concludes that the determination of the diastase content of the cerebrospinal fluid is of no practical value.

Robinson and Miller [39] discuss the differentiation between discoloration of the cerebrospinal fluid due to bleeding into the subarachnoid space and that due to compression of the spinal cord. In the former case, they say, the cerebrospinal fluid will give a positive reaction to the benzidine test, whereas in the latter instance it will give a negative reaction.

THE SOCIAL AND PUBLIC HEALTH ASPECTS OF SYPHILIS

Dissemination of Information.—Anything approaching a complete summary of the publications directed toward education of the public on the basic facts concerning syphilis is beyond the scope of this review. One editorial comment,[40] however, summarizes the conservative view of the situation:

> Publicity as to syphilis is now becoming widespread. Until recently, except for a brief three year period, nothing about the disease, not even its name, could be forced into the public press. Within the last two years, conservative and liberal newspapers and magazines alike . . . had mentioned "syphilis" and had printed news stories, editorials or important feature articles concerning it. Now books are being published for the public and at least three leading magazines have scheduled articles for early appearance. In journalistic parlance, the subject is "hot."
>
> Every one knows that a flood of misinformation may do more harm than good. Overemphasis on moral reform, on "social hygiene," and underemphasis on the more easily defensible medical approach are possibilities. Even more dangerous is the publication of such scientific misinformation as suggests (*Literary Digest*, Oct. 31, 1936) that syphilis may be "cured" by one inadequately studied method of treatment in three months, or by another in two weeks.

---

36. Stary, Z.; Kral, A., and Winternitz, R.: Zur Chemie den Liquorreaktion nach Pándy, Ztschr. f. d. ges. Neurol. u. Psychiat. **157**:116 (Jan. 12) 1937.

37. Deadman, W. J.; Elliott, F. J., and Smith, H.: The Examination of Cerebrospinal Fluids by Colloidal Carbon, Am. J. Clin. Path. **7**:246 (May) 1937.

38. Donati, F.: Il contenuto diastasico del liquor nelle malattie sifilitiche del nevrasse, Gior. di clin. med. **16**:1296 (Oct. 30) 1935.

39. Robinson, F. H., and Miller, B. N.: On the Differentiation of Colored Cerebrospinal Fluids, Am. J. M. Sc. **191**:538 (April) 1936.

40. Education of the Public on Syphilis—A Warning! editorial, J. A. M. A. **108**:478 (Feb. 6) 1937.

Another serious danger is the fact that the publicity gives evidence of being concentrated within too short a period. Since current public interest is greater than can be satisfied by medical accomplishment, interest may evaporate faster than it can be appeased. Those who wish to educate will have shortly said all there is to say and will have nothing new to offer, only repetition. Editors and audience alike will treat the subject as the latest fad, wearying of it as quickly as they have wearied of such other great American fads as flagpole sitting or miniature golf. It is possible, and at the present rate likely, that the syphilis control program will be talked to death.

The dissemination of information to the members of the medical profession has been as energetically pursued and perhaps more judiciously managed. Vonderlehr [41] summarizes the development of the program for the control of venereal disease, no small feature of which is provision for the training of those who wish to become proficient and the dissemination of information to members of the medical profession as a whole. Much of this has been by word of mouth, but Stokes [42] has done yeoman service in making authoritative information available to all who care to read. Vonderlehr and Usilton [43] present the statistical point of view. They bring out that 100,000 adolescent children annually acquire syphilis before they are self-supporting and emphasize that the financial burden of the proper treatment of this group must not be left on the already overburdened shoulders of the practitioner; it must be shared by the local health officer, who also usually is in the best position to conduct the necessary contact investigation.

Moore [44] points out that the ultimate control of syphilis depends on the development of adequate facilities for treatment. Parran [45] properly remands the problem to the practitioner:

In the public health control of syphilis, the members of the . . . [medical profession] have an opportunity each in his own community, to sponsor and support a great work for a high purpose, with assurance of good results to the public.

41. Vonderlehr, R. A.: Recent Extension of Venereal Disease Control Work Through the Provisions of the Social Security Act, Pub. Health Rep. **52**:95 (Jan. 22) 1937.

42. Stokes, J. H.: (*a*) Education of Physician and Movement for Venereal Disease Control, J. A. M. A. **107**:866 (Sept. 12) 1936; (*b*) The Control of Syphilis: Critical Examination of Some of Its Problems (Prosser White Oration), Brit. J. Dermat. **48**:527 (Nov.) 1936; (*c*) The Control of Syphilis, Ven. Dis. Inform. **17**:315 (Nov.) 1936; (*d*) Clinical Problems in Syphilis Control Today, J. A. M. A. **108**:780 (March 6) 1937.

43. Vonderlehr, R. A., and Usilton, L.: The Mass Control of Syphilis, South. M. J. **30**:281 (March) 1937.

44. Moore, J. E.: Development of Adequate Treatment Facilities for Control of Syphilis, J. A. M. A. **107**:787 (Sept. 5) 1936.

45. Parran, T., Jr.: Public Health Control of Syphilis, Ann. Int. Med. **10**:65 (July) 1936.

The Prevalence of Syphilis.—There is no new information about either the incidence or the prevalence of syphilis based on a large scale study such as that of Usilton's [46] survey of the incidence and prevalence of syphilis and gonorrhea. Isolated reports of selected groups of the population indicate, however, that the accepted figures are of the correct order of magnitude. Bell [47] reports that somewhere between 3 and 25 per cent of the sick of Dallas, Texas, have syphilis. Roberts and Williams [48] conducted a survey to determine the prevalance of syphilis in Gibson County, Tenn. They rather wryly report that in spite of a program for the control of syphilis which has been in operation for ten years, the rate of prevalence of syphilis is 1.7 per cent for the white population and 10.8 per cent for the Negroes. Holloway, Grant and Bent [49] determined the incidence of positive results of serologic tests for syphilis in two groups of Negroes—clinic patients and a group of well students. Unfortunately, the arbitrary selection of material makes their study of little value for estimating the general incidence or prevalence of syphilis in the Negro population.

Scattered reports from abroad (excluding the Scandinavian countries) suggest that syphilis is as common there as here. Jósa [50] found that 5 per cent of nearly 20,000 patients who were admitted to the surgical clinic of the Debrecen Hospital, Hungary, showed a positive reaction to a serologic test for syphilis. Hughes,[51] however, discovered positive reactions to serologic tests for syphilis for only just over 1 per cent of Australian women who were pregnant.

The Functions of the Health Department in the Control of Syphilis.—Reinhard [52] offers a plea against a selective policy which serves to exclude patients with latent syphilis from treatment in health department clinics. He points out that this group presents an important and potentially serious problem if no facilities are provided by which the crippling

46. Usilton, L. J.: Prevalence of Venereal Disease in the United States, Ven. Dis. Inform. **11**:543 (Dec. 20) 1930.

47. Bell, M. D.: The Incidence of Syphilis in Dallas and Vicinity as Determined by Serological Methods: An Analysis of More than 39,000 Cases, Texas State J. Med. **32**:753 (March) 1937.

48. Roberts, F. L., and Williams, W. C.: The Results of a County-Wide Survey and an Outline of the Syphilis Control Program in Gibson County, Tenn., South. M. J. **30**:458 (May) 1937.

49. Holloway, G. D.; Grant, W. H., and Bent, M. J.: The Incidence of Syphilis in the Negro as Indicated by Serologic Tests, Am. J. Syph., Gonor. & Ven. Dis. **21**:303 (May) 1937.

50. Jósa, L.: Die Bedeutung der Syphilis in der Chirugie auf Grund serologischer Untersuchungen, Arch. f. klin. Chir. **184**:299, 1935.

51. Hughes, T. D.: The Result of the Routine Use of the Wassermann Test in 3,404 Patients Attending for Antenatal Care, M. J. Australia **2**:783 (Dec. 5) 1936.

52. Reinhard, F. O.: Late Latent Syphilis—A Problem and a Challenge, J. Social Hyg. **22**:360 (Nov.) 1936.

late lesions of syphilis may be prevented from developing. Vonderlehr [53] reemphasizes that the primary function of the Public Health Service and related agencies in the control of venereal disease is cooperation with the private practitioner.

Programs for Syphilis Control Abroad.—Freeman [54] recapitulates the Danish program for control of venereal disease, Vassaf [55] describes the campaign for the control of syphilis in Turkey, Yarros [56] is impressed by the accomplishments of the program in Moscow and Werr [57] proudly points to the healthier and happier families of Germany today.

Syphilis and Life Insurance.—In order to discover what life insurance companies are doing about syphilis Rein, Le Moine and Stephens sent a questionnaire to ninety-seven companies. Their present report [58] is based on the seventy-five replies which they received. Fifty-six (75 per cent) of those who replied stated that they occasionally requested a serologic test for syphilis "on suspicion," but only four companies had requested more than 100 tests in the preceding year. Twenty-four companies had requested less than 10 or "very few" tests in the same period.

Many of the respondents gave their reasons for not utilizing serologic tests for syphilis more frequently. These reasons fall into three groups: (1) the difficulty and expense which preinsurance serologic testing as a routine would involve, (2) the undesirable effect on the client which would be produced by demanding a serologic test and (3) the needlessness of making blood tests as a routine procedure.

In examining the implications contained in their findings the authors bring out some startling facts: Estimating that during 1935 about 2,500,000 persons applied for ordinary life insurance in the seventy-five companies and that probably 2 or 3 per cent of these had syphilis, the authors arrive at the conclusion that there were about 50,000 syphilitic applicants during the year which they are considering (1935). Only about 250 of these cases were detected!

---

53. Vonderlehr, R. A.: The Relationship of the Venereal Disease Control Work of the United States Public Health Service to the Physician in Private Practice, Am. J. Syph., Gonor. & Ven. Dis. **21**:32 (Jan.) 1937.

54. Freeman, C. W.: Venereal Disease Control in Denmark, with Special Reference to Control of Syphilis, J. Social Hyg. **23**:189 (April) 1937.

55. Vassaf, E.: The Syphilis Campaign in Turkey, J. Social Hyg. **23**:213 (April) 1937.

56. Yarros, R. S.: Moscow Revisited: Social Hygiene 1930-1936, J. Social Hyg. **23**:200 (April) 1937.

57. Werr, F.: Die Geschlechtskrankheiten im Ehegesundheitsgesetz, Dermat. Wchnschr. **104**:105 (Jan. 23) 1937.

58. Rein, C. R.; Le Moine, M., and Stephens, M. G.: What Are Life Insurance Companies Doing About Syphilis? J. Social Hyg. **23**:258 (May) 1937.

Syphilis in Industry.—Gehrmann [59] reports the results of serologic tests for syphilis on 36,794 employees of a large corporation. Four per cent (1,488) were found to show a positive reaction. This author was particularly interested, however, in the course of events after a positive reaction to a serologic test for syphilis had been discovered. All positive reactions were verified. With few exceptions the result of the test was a matter of confidence between the employee and the laboratory. Each employee who manifested a positive reaction was referred to his physician or to a clinic for treatment. In following these patients to determine the adequacy of the treatment they had received, the author found the greatest variation in practice. Some physicians had refused to treat the patients, others were treating with pills alone while still others were extracting incommensurate fees from the luckless patients.

Syphilis and Unemployment.—Syphilis in relation to employment has been the subject of editorial comment: [60]

> A potentially serious social situation is in process of creation by virtue of the current medical and lay interest in the campaign to control syphilis. The medical directors of certain large industrial corporations, and certain branches of the Federal Government itself, presumably stimulated by the recent wide publicity given to syphilis, are requiring routine blood tests of all applicants for positions, and are refusing employment to those found to have positive serologic tests for syphilis. In some instances, individuals already employed have been tested and, if found to be infected, dismissed.
>
> The reason assigned for this procedure by certain corporation medical directors and lay officials who have been questioned regarding it are threefold (1) the danger of transmission of syphilis to others (e. g., by food handlers); (2) the risk that a syphilitic person handling dangerous machinery may endanger the lives of others; and (3) the additional economic risk imposed upon the company by the possibility that the syphilitic individual may become disabled directly or indirectly because of his syphilis, thus imposing, through various forms of industrial compensation or other types of social insurance, the burden of his care upon the company (or Federal Government).
>
> It is easy for the physician familiar with syphilis to show that, as related to the use of the routine blood test as a standard for employment, these arguments are fallacious.
>
> (1) The danger of transmission of syphilis through nonsexual contact is slight indeed . . . Whatever small risk of infecting others may exist is for all practical purposes limited to the period before the diagnosis is made, and is over as soon as treatment is started . . .
>
> (2) The risk that a syphilitic person handling dangerous machinery may endanger the lives of others is, for all practical purposes, limited to patients with cardiovascular or with neurosyphilis, and more particularly to those with

59. Gehrmann, G. H.: Syphilis in a Large Industrial Organization, Ven. Dis. Inform. **17**:227 (Aug.) 1936.

60. Syphilis and Unemployment, editorial, Am. J. Syph., Gonor. & Ven. Dis. **21**:339 (May) 1937.

paresis. There is not the slightest evidence to indicate that industrial accidents are more frequently due to the carelessness of syphilitic persons (excluding the two classes named) than to that of nonsyphilitic workers. The routine positive blood test does not establish the diagnosis of cardiovascular or neurosyphilis. These diagnoses can be reached only after complete study of the patient . . .

(3) The additional economic risk imposed upon the company by industrial compensation or other forms of social insurance is the greatest objection to the employment of syphilitic persons. In this field the sweeping decision not to employ or to dismiss syphilitic individuals is based on inadequate information; or, if particular corporations do have adequate data covering the point, these data have not been made freely available in medical literature.

So far as is known, there is (except in rare instances) no good evidence to indicate that a syphilitic worker who does not have cardiovascular or neuraxis involvement is any more likely (*a*) to be involved in accidents than his nonsyphilitic brother; or (*b*) if involved in an accident, to suffer any more serious or prolonged disability; or (*c*) to suffer more severely from intercurrent nonsyphilitic disease; or even (*d*) to undergo material shortening of his life span. Whatever risk there may be of any of these eventualities may be largely guarded against (except in cardiovascular or neurosyphilis) by adequate treatment . . .

The procedure by which an employer can best protect himself against possible loss from syphilis, and at the same time best serve society, is not therefore wholesale refusal to employ syphilitic workers, but individualization in each particular case. . .

Finally, there are grave medical and social objections to class discrimination in the use of the routine blood test. There is no adequate reason why this test should be limited to individuals employed in minor capacities. The paretic executive is perhaps more likely to do harm to affairs of the company than the comptometer operator or the common laborer with latent syphilis. If industry is to be consistent in this matter, it will begin the performance of routine serologic tests for syphilis with the president of the company, the board of directors, and the medical director, and will include all executives regardless of age, sex, salary, education, or social position. If the laborer is to be fired solely because he has syphilis, so should the syphilitic executive be fired.

The Epidemiology of Syphilis.—The value of contact investigation in the control of syphilis has long been recognized. It is unfortunate that application of this method of case finding in many places has been somewhat handicapped by lack of personnel and a feeling of futility. Kulchar and Ninnis [61] show, however, that every effort is worth while. These authors attempted to trace the contacts of 244 patients with early syphilis. By so doing they discovered 113 additional cases of fresh infection. The Spillmanns [62] emphasize the time factor in the epidemiology of syphilis. On the appearance of the fifth man to give a history of infection by a blond prostitute, search for her was begun. Before

61. Kulchar, G. V., and Ninnis, E. I.: Tracing the Source of Infection in Syphilis, J. Social Hyg. **22**:370 (Nov.) 1936.

62. Spillmann, L., and Spillmann, A.: Résultats des enquêtes épidémiologiques effectuées dans le but de préciser l'origine des contaminations syphilitiques, Bull. Soc. franç. de dermat. et syph. **43**:1360 (July) 1936.

she was found, however, at least 9 others had acquired syphilis from her. Church [63] graphically presents the tragedies which may result from failure to follow contacts.

The investigation of contacts is not, however, always easy. The patient frequently is neither ready to disclose the name of his sexual partner nor willing to bring the partner to a physician or a clinic. Ingraham [64] has been successful in overcoming this natural reticence by a technic which she describes as the persuasive approach:

> Its aims with the syphilis patient are to gain his voluntary disclosure of identities of recent sexual intimates, to gain his voluntary services in personally recruiting them for medical examination, and to gain his voluntary agreement to our performance of this service. On the part of the "contact" the objective is that he voluntarily seek medical examination for syphilis. A trial of this noncompulsive method was rewarded with confidential disclosures from infected patients as to names and whereabouts of contacts and these were induced to be examined for syphilis as follows:
>
> 1. Of 201 patients with syphilis, 114 identified 174 exposures, an identification rate of 1.5 per cent contacts per productive case.
>
> 2. One hundred and thirty-seven [64a] (80 per cent) of the 174 persons sought were located; 128 (73.5 per cent) were recruited for examinations. Since 128 of the 139 [64a] contacts located were persuaded to report for study persuasion was 92 per cent effective when the individual contact could be personally reached.
>
> 3. The type of community has little effect on the response of individuals, as evidenced by a comparison of these figures with those obtained by other writers elsewhere.

Brumfield [65] provides a succinct summary of the salient features of the problem.

The Sources of Syphilitic Infection.—Americans are so imbued with the Calvinistic theosophy that it is difficult for them to face and deal with facts which carry any taint of the immoral. It is perhaps for that reason that the only recent study of the source of syphilitic infection comes from Touraine and Chon.[66] In their experience in two large dispensaries in Paris these authors encountered 617 patients with recently acquired syphilis. In this group there were 385 men and 232

63. Church, F. H.: Transmission and Effects of Syphilis, M. Rec. **144**:323 (Oct. 7) 1936.

64. Ingraham, L. B.: The Persuasive Approach with the Infectious Syphilis Carrier: A Study in Public Health Method, J. A. M. A. **107**:1990 (Dec. 12) 1936.

64a. The discrepancy between these figures is not clear. From the original text apparently 139 contacts were located.

65. Brumfield, W. A., Jr.: The Epidemiologic Aspects of Syphilis Control, South. M. J. **30**:82 (Jan.) 1937.

66. Touraine, M. A., and Chon: Les sources de contamination syphilitique (statistique personelle d'après deux dispensaries), Bull. Soc. franç. de dermat. et syph. **44**:689 (April) 1937.

women. Half the men had acquired the disease from street-walkers; most of the others had been infected during contacts thought to be safe. The women, however, reported such variegated histories that few generalizations were possible.

DRUGS

General Principles.—Cole,[67] in a general discussion of the pharmacotherapeusis of syphilis, especially emphasizes four of the characteristics which a desirable antisyphilitic remedy should possess, once the necessary facts regarding its toxicity and therapeutic index are known:

1. It should be cheap and readily available.
2. It should be simple in form and in technic of administration.
3. It should produce a minimum of untoward reactions, either immediate or delayed.
4. It should be rapid in action.

Throughout, this author takes the conservative stand regarding the adoption of new drugs or new principles in syphilotherapy and, for example, says concerning acetarsone: "As yet I am unwilling to recommend the indiscriminate use of acetarsone in the treatment of congenital syphilis. It is still too much in the experimental stage." To this statement Traisman[68] takes violent exception. In reply Cole[69] carefully restates the proper attitude of conservatism to be adopted toward a new antisyphilitic remedy and gives the three reasons for his opinion of acetarsone:

1. The antisyphilitic value of the drug is unproved.
2. Published reports indicate that the drug is highly toxic.
3. The use of acetarsone purports to do nothing which may not readily be accomplished by other means the worth of which is established.

Rothermundt,[70] in an undocumented discussion of methods for the evaluation of antisyphilitic remedies, deprecates the value of biologic testing. Only by clinical use, he says, may the value of an antisyphilitic drug be determined.

---

67. Cole, H. N.: The Pharmacopeia and the Physician: The Use of Antisyphilitic Remedies, J. A. M. A. **107**:2123 (Dec. 26) 1936.

68. Traisman, A. S.: The Use of Antisyphilitic Remedies, J. A. M. A. **108**: 825 (March 6) 1937.

69. Cole, H. N.: The Use of Antisyphilitic Remedies, J. A. M. A. **108**:825 (March 6) 1937.

70. Rothermundt, M.: Ueber die Bedeutung der biologischen Prüfung der Salvarsane, Deutsche med. Wchnschr. **62**:647 (April 17) 1936.

Cannon [71] and Harrison,[72] on the basis of their wide personal experiences in syphilotherapy, speak for the superiority of arsphenamine over its derivatives in the treatment of patients with early syphilis. Harrison is reconciled to the abandonment of arsphenamine because of the difficulties attending its administration. Cannon, however, seeks ways to obviate or minimize these difficulties and so to retain the most potent drug in general use.

Moore and his collaborators [73] report the results of a comparison of the rate of reversal of the reactions to quantitatively titered complement fixation tests for patients with early syphilis who were under treatment with various drugs. In a discussion of the general principles involved they say:

> The evaluaton of the worth of any antisyphilitic drug in man depends on a number of factors, some readily determinable within a few weeks of observation, others requiring shorter or longer periods ranging from a few months to a lifetime. The more important of these, assuming the factors of toxicity and general drug tolerance to be approximately equal, are:
>
> 1. The rate of disappearance of surface organisms from the moist lesions of early syphilis.
> 2. The rate of healing of visible early and late lesions (or of symptomatic response in such conditions as neurosyphilis).
> 3. The rate of reversal of serologic reactions in early syphilis.
> 4. The proportion of serologic resistance, i. e., Wassermann fastness, in early and late syphilis.
> 5. The incidence of abnormal spinal fluids in treated patients with early syphilis.
> 6. The incidence of serologic relapse in early syphilis.
> 7. The incidence of early clinical relapse, especially infectious mucocutaneous relapse and neurorecurrence.
> 8. The incidence of late progression or relapse.
> 9. The permanence of clinical and serologic normality.
>
> The value of a given drug in the first of these respects may be determined within a few days; as to the second and third, within a few weeks; as to the fourth, fifth, sixth, and seventh, within a period ranging from a few months to three or four years; and as to the eighth and ninth, within many years to a lifetime. It is quite possible, furthermore, that a drug may be active in accomplishing disappearance of surface organisms, healing of lesions, and rapidity of early

71. Cannon, A. B.: Optimal Treatment for Early Syphilis, Based on a Twenty Year Trial of Arsphenamine, Bismuth and Mercury Preparations, Am. J. Syph., Gonor. & Ven. Dis. **21**:155 (March) 1937.

72. Harrison, L. W.: Experiences with Antisyphilitic Treatment from the Pre-Salvarsan Era to the Present and Their Possible Bearing on Present Treatment Practice, Brit. J. Ven. Dis. **13**:1 (Jan.) 1937.

73. Moore, J. E.; Hardy, S. M.; Robinson, H. M., and Eagle, H.: The Response of the Quantitatively Titered Wassermann Test in Early Syphilis to Treatment with Five Different Arsenical Drugs, Am. J. Syph., Gonor. & Ven. Dis. **20**:503 (Sept.) 1936.

serologic reversal, and yet be relatively unsatisfactory in respect to the other criteria named, and in particular to the most important of them all, the permanence of clinical and serologic normality.

It will be noted that with few exceptions, the requirements enumerated apply almost exclusively to early syphilis. Excepting only the pentavalent arsenicals (tryparsamide, acetarsone), it is true of all the other drugs used in syphilotherapy (i. e., the trivalent arsphenamines, bismuth, and mercury) that their action in early syphilis is a reliable index of what may be expected of them in late syphilis. It is particularly true that so far as the rate of serologic reversal is concerned, early syphilis must be chosen as the prototype.

They found that the average reduction in the titer of the complement fixation test in the blood of patients with early syphilis was approximately the same for treatment with four of the five drugs studied (arsphenamine, silver arsphenamine, bismarsen and mapharsen). The patients treated with neoarsphenamine, however, exhibited a somewhat slower reduction in reagin titer. These authors conclude, therefore, that since these five drugs are not of equal value with respect to other important results of treatment, the rate of serologic reversal for patients with early syphilis after treatment with a given drug can be regarded only as a relatively unimportant factor in the final evaluation of that drug.

Mapharsen.—Since the publication of the original reports, previously referred to,[1] there has accumulated a considerable body of experience with the use of mapharsen in syphilotherapy. The largest series of patients treated with mapharsen is presented by Gruhzit, Dixon and their collaborators,[74] who report the results of the administration of 75,589 injections of the drug to 4,841 patients. These authors observed no severe reactions to the treatment in this series, and there were no deaths. Moderately severe reactions, which were almost entirely gastro-intestinal, occurred at the rate of 4.4 per thousand injections. To these authors the clinical and serologic outcome for the group as a whole was satisfactory, as compared with the expected course under other methods of treatment.

Kulchar and Barnett[75] present a detailed analysis of the results which they observed from the administration of 1,270 doses of mapharsen to 56 patients with early syphilis. They found that surface lesions of these patients healed more rapidly than those of patients treated with neoarsphenamine but that serologic reversal occurred more slowly than in the series of patients with early syphilis who had received arsphenamine who

74. Gruhzit, O. M.; Dixon, R. S., and others: Mapharsen in Mass Treatment of Syphilis in a Clinic for Venereal Diseases, Arch. Dermat. & Syph. **34**:432 (Sept.) 1936.

75. Kulchar, G. V., and Barnett, C. W.: Mapharsen in the Treatment of Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:482 (Sept.) 1936.

were reported on by Moore and Kemp.[76] Increased sensitivity of the serologic tests now employed, however, may well explain this apparent difference. The incidence of neurosyphilis they found to be no less than that in groups of patients treated by other methods. One unusual feature of the experience of these authors was the high incidence (14.7 per cent) of gastro-intestinal reactions.

Astrachan [77] observed 158 patients treated with mapharsen. Twenty-five of them had early syphilis, and the rate of healing of lesions was compared to that produced by neoarsphenamine. From his results he concludes that mapharsen, while a useful antisyphilitic remedy, is less potent than neoarsphenamine. Its use, he says, should therefore be limited to the treatment of patients with latent or late syphilis.

Miller, Epstein and Simpson [78] discovered among 400 patients 31 who were intolerant to neoarsphenamine but who were given mapharsen without event and 2 for whom the reverse was true. In addition, there were 6 patients who were intolerant to both drugs.

Wieder and the Foersters [79] extend their earlier observations, which were reviewed previously,[1] and again conclude that mapharsen is a potent antisyphilitic remedy, with special properties which justify its continued use and study over an extended period. Essentially similar conclusions are reached by Peterson,[80] Schmidt and Taylor [81] and Parsons.[82]

Triarsen.—Stokes and Beerman [83] report the observation of 189 patients who were given a total of 3,009 injections of triarsen. From the results they conclude that this drug is suitable for use in the treatment of patients with early syphilis. Certain of its properties, however, they feel should be studied further.

---

76. Moore, J. E., and Kemp, J. E.: The Treatment of Early Syphilis, Bull. Johns Hopkins Hosp. **39**:36 (July) 1926.

77. Astrachan, G. D.: Mapharsen in Antisyphilitic Therapy: Preliminary Report; a Study Based on 3,386 Injections of Mapharsen, Am. J. Syph., Gonor. & Ven. Dis. **21**:81 (Jan.) 1937.

78. Miller, H. E.; Epstein, N. N., and Simpson, R. G.: Mapharsen: Its Use in the Treatment of Syphilis, California & West. Med. **45**:321 (Oct.) 1936.

79. Wieder, L. M.; Foerster, O. H., and Foerster, H. R.: Mapharsen in the Treatment of Early Syphilis: Further Experiments, Arch. Dermat. & Syph. **35**: 402 (March) 1937.

80. Peterson, S. C.: The Use of Mapharsen in the Treatment of Syphilis, Canad. M. A. J. **36**:172 (Feb.) 1937.

81. Schmidt, E. E., and Taylor, G. G.: The Treatment of Syphilis with Mapharsen, Am. J. Syph., Gonor. & Ven. Dis. **21**:402 (July) 1937.

82. Parsons, R. P.: An Estimate of Arsenoxide (Mapharsen) in the Treatment of Early Syphilis, U. S. Nav. M. Bull. **35**:207 (April) 1937.

83. Stokes, J. H., and Beerman, H.: New Arsphenamine Synthetics in Treatment of Syphilis: A Consideration of Test Procedure and of a New Drug (Triarsen), Arch. Dermat. & Syph. **35**:78 (Jan.) 1937.

Tryparsamide.—Vonkennel and Kimmig [84] report attempts to demonstrate arsenic in the cerebrospinal fluid after the intravenous injection of therapeutic doses of tryparsamide. No arsenic could be recovered from the cerebrospinal fluid of any of 16 patients so treated. Further investigation showed also that this apparent impermeability of the blood-brain or blood-cerebrospinal fluid barrier was not altered after therapeutic malaria.

Bismuth.—In his general discussion of syphilotherapy Cole [07] points out that there are many bismuth preparations available and advises the physician to learn the action of but a few of the well tried ones of known dependability. For use as a routine he advises a suspension of bismuth subsalicylate in oil, because of its slow, constant action. Under circumstances in which a more rapid action is desired, the use of one of the water-soluble preparations is recommended, but the author emphasizes that for therapeutic effectiveness these must be given thrice weekly.

Hanzlik [85] objects to the use of insoluble bismuth compounds on certain theoretical grounds but offers no facts to substantiate his opinion.

Johnson and Barnett [86] report the results of the examination of the cerebrospinal fluid of 120 patients with early syphilis who had received iodobismitol to the exclusion of other heavy metal preparations, in alternation with courses of neoarsphenamine or mapharsen. They discovered that 16 patients (13 per cent) had an abnormal cerebrospinal fluid. This coincided so closely with the incidence of neurosyphilis (13.8 per cent) in patients with early syphilis observed by Moore and Faupel [87] that the authors conclude:

> The substitution of iodobismitol for other heavy metal preparations in the routine treatment of patients with primary and secondary syphilis does not eliminate the problem of central nervous system involvement.

The rationale of prohibiting the use of alcoholic beverages by patients with syphilis, especially neurosyphilis, is called into question by the experimental observations of Newman and Richardson.[88] These authors

84. Vonkennel and Kimmig: Arsenbestimmungen im Liquor nach Verabreichung fünfwertiger Arsenpräparate, Klin. Wchnschr. **16**:603 (April 24) 1937.

85. Hanzlik, P. J.: Insoluble Bismuth Compounds in Antisyphilitic Treatment, J. A. M. A. **106**:1985 (Dec. 12) 1936.

86. Johnson, G. S., and Barnett, C. W.: The Effect of Iodobismitol upon Spinal Fluid Findings in Early Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**: 651 (Nov.) 1936.

87. Moore, J. E., and Faupel, M.: Asymptomatic Neurosyphilis: V. A Comparison of Early and Late Asymptomatic Neurosyphilis, Arch. Dermat. & Syph. **18**:99 (July) 1928.

88. Newman, H. W., and Richardson, A. P.: The Effect of Alcohol on Penetration of Bismuth into the Central Nervous System, Am. J. Syph., Gonor. & Ven. Dis. **21**:77 (Jan.) 1937.

were able to demonstrate traces of bismuth in the subarachnoid fluid of 2 of 3 dogs which had received 6 biweekly injections of 0.05 cc. of iodobismitol per kilogram of body weight (the usual therapeutic dose for man) and daily during this period had ingested 10 cc. of ethyl alcohol per kilogram. No bismuth could be found, however, in the subarachnoid fluid of 3 control animals which had received the same doses of iodobismitol but no alcohol. Further, in a more extensive series of experiments they compared the bismuth content of the blood, brain, cerebrospinal fluid and spinal cord of 8 dogs to which iodobismitol had been given biweekly in doses of 0.5 cc. per kilogram until death occurred or for four weeks. Half the dogs also received 10 cc. of ethyl alcohol daily; the remainder had none. The results are somewhat variable, owing in part at least to the technical difficulties of accurately estimating small quantities of bismuth in organic material. The authors feel, however, that they have shown that ingestion of alcohol under the circumstances of their experiments definitely increases the penetration of bismuth into the central nervous system.

Ko [89] describes two small groups of experiments in which he treated syphilitic rabbits by rubbing an ointment containing 2 per cent bismuth into the back. The results were extremely variable, but in the latter series a cure was obtained in 2 of 3 animals by 11 inunctions.

The group headed by Hanzlik have for many years been engaged in study of the chemistry and pharmacology of bismuth compounds for the treatment of syphilis, and in their most recent communications they [90] present a preliminary report concerning a new bismuth product. Sodium bismuthate, the compound which they employed, is not new; their contribution rests in having devised a method for taking it into solution to form what they term sodium bismuthate soluble, or sobisminol. The technic of preparation of the product consists essentially in dissolving sodium bismuthate in triisopropanolamine and with appropriate precautions adding propylene glycol and water to a final concentration of 3 per cent sodium bismuthate, 8 per cent triisopropanolamine and 50 per cent propylene glycol. The resulting solution is stable, it does not precipitate protein and by appropriate experiments it was shown to be well tolerated on intramuscular injection or oral administration by

89. Ko, H.: The Effect of Inunction Treatment with Bismuth Organosol Salve in Experimental Rabbit Syphilis, Lues: Bull. Soc. japon de syph. **14**:22 (Dec.) 1936; The Effect of Inunction Treatment with Bismuth Organosol Salve in Experimental Syphilis, ibid. **15**:7 (April) 1937.

90. (*a*) Hanzlik, P. J.: Sodium Bismuthate Soluble in Experimental Syphilis, J. Pharmacol. & Exper. Therap. **59**:328 (March) 1937. (*b*) Hanzlik, P. J.; Lehman, A. J., and Richardson, A. P.: Sodium Bismuthate Soluble: A New Product for Intramuscular and Oral Administration in the Treatment for Syphilis; a Preliminary Summary Report, Am. J. Syph., Gonor. & Ven. Dis. **21**:1 (Jan.) 1937.

experimental animals and by both normal men and men with syphilis. In the treatment of rabbits with experimental syphilis the therapeutic index of sobisminol given by intramuscular injection was found to be not less than 10 and probably to be 15 or greater.[90a]

The results of the observations on both normal human beings and those with syphilis treated with sobisminol [90b] indicate that the drug is absorbed after either oral or intramuscular administration, that it is an effective antisyphilitic remedy and that its toxicity is low. Hanzlik believes, therefore, that sobisminol is entitled to extensive clinical trial, especially with regard to its suitability for the oral treatment or prophylaxis of syphilis.

Kolmer, Brown and Rule [91] present a survey of the problems of evaluation of the oral administration of bismuth compounds and report the results of their investigations on the oral administration of bismuth and potassium tartrate to rabbits. They found that in spite of the high acidity of the stomach contents of the rabbit the drug was absorbed in therapeutically effective amounts.

"Arsenical 190."—Tatum and his collaborators [92] present the results of an experimental and clinical study of arsenical 190,3-amino-4-betahydroxyethoxyphenylarsonic acid, which for administration is prepared as the sodium salt. Experimentally, the drug was found to be much superior to tryparsamide both in trypanosomiasis and in rabbit syphilis. Clinically, 128 patients with various forms of syphilis were given a total of 2,515 injections, usually of the optimum dose of 3 Gm. The drug was found to be effective in every stage of syphilis, but particularly in neurosyphilis, in which it appeared to be superior to tryparsamide. The incidence of toxic amblyopia was so high, however, that the drug is not recommended. In addition to the frequent occurrence of subjective reactions, in 16 patients objective changes developed in the visual fields or optic disks, 2 became blind and a third lost useful vision. The authors point out that this toxicity for the optic nerve is not unexpected, because of the existence of an amino group in the meta position to arsonic acid.

Neocryl.—At the request of the Medical Research Council of Great Britain, Yorke and Murgatroyd [93] investigated the properties of sodium

91. Kolmer, J. A.; Brown, H., and Rule, Anna M.: The Oral Administration of Potassium Bismuth Tartrate in the Treatment of Experimental Syphilis of Rabbits, with a Note on the Gastric Chemistry of the Rabbit, Am. J. Syph., Gonor. & Ven. Dis. **21**:387 (July) 1937.

92. Tatum, A. L.; Pfeiffer, C. C.; Kuhs, M. L.; Lorenz, W. F., and Green, J. T., Jr.: A Study of the Sodium Salt of 3-Amino-4-Beta-Hydroxyethoxyphenylarsonic Acid in Experimental Trypanosomiasis and Syphilis and in Clinical Syphilis and Neurosyphilis, J. Pharmacol. & Exper. Therap. **59**:241 (March) 1937.

93. Yorke, W., and Murgatroyd, F.: A New Arsenical for the Treatment of Syphilis and Trypanosomiasis, Brit. M. J. **1**:1042 (May 23) 1936.

succinanilomethylamide-p-arsonate, which is supplied in continental Europe under the name neocryl and which is being introduced in Great Britain as "crylarsan." In experimental animals the drug was found to be less toxic than tryparsamide and to possess somewhat greater trypanocidal activity. By man the drug is well tolerated when administered in the same dose and in the same long courses customary in treatment with tryparamide. In a large experience no visual disturbances or other serious reactions were observed. The authors warn, however, that the chemical nature of the drug presents a risk of visual reactions. Clinically, they found the action of the drug similar to that of tryparsamide in patients with neurosyphilis, but in contrast with tryparsamide, this drug possesses some effectiveness on other lesions of syphilis, both early and late.

Mercury.—Wright [94] presents a complete review of the use of mercury in syphilotherapy and concludes:

> Mercury must still be looked upon as a valuable syphilitic agent and probably will always retain a place in the ever growing list of antisyphilitic remedies.

Acetarsone.—Rosahn and Kemp [95] review the literature regarding the oral administration of acetarsone in the treatment of syphilis in human beings and experimental animals and report the results of their experience in treating 53 syphilitic rabbits. They say:

> A review of the literature and our own investigations point to one outstanding conclusion; namely, that the toxicity of orally administered 3-acetylamino-4-hydroxyphenylarsonic acid as it is now manufactured is so variable as to preclude its use in the rabbit.

This variability, they point out, may be either in the drug or in the animal and its biologic reactions. The latter they think most likely. Whatever it is, it renders the drug entirely unsuitable for use in the treatment of rabbit syphilis, and by analogy these authors argue that the drug is likewise unsuitable for use by human beings with syphilis.

Rhodium.—Jahnel [96] provides an interesting report of the use of rhodium compounds in the treatment of experimental syphilis in the rabbit. Rhodium chloride or sodium rhodium chloride was utilized for intramuscular injection in doses of 0.05 or 0.1 Gm. per kilogram of body weight. The sodium salt was more effective, and especially after the larger dose dramatic healing of lesions occurred. The compounds are of low toxicity; both were found to have a therapeutic index of more than 12.5. They may, however, produce local irritation at the site

94. Wright, C. S.: Mercury in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:660 (Nov.) 1936.

95. Rosahn, P. D., and Kemp, J. E.: The Oral Administration of Stovarsol in the Treatment of Experimental Syphilis of the Rabbit, Am. J. Syph., Gonor. & Ven. Dis. **21**:180 (March) 1937.

96. Jahnel, F.: Ueber die Heilwirkung von Rhodiumverbindungen bei der experimentellen Syphilis und Framboesie, Klin. Wchnschr. **16**:657 (May 8) 1937.

of injection. Rhodium is expensive, but Jahnel feels that the experience is sufficiently encouraging to justify further experimental work. He does not feel, however, that there is yet enough information to warrant clinical trial of the rhodium compounds.

UNTOWARD EFFECTS OF TREATMENT

Cook and Wingo [97] seized the opportunity to determine the incidence of reactions to intravenous treatment of syphilis in the large experience of the Medical Department of the Navy and to compare the reaction rate for the year 1935 with that in the period since 1925. Over the entire period of eleven years there were given almost 1,000,000 doses of neoarsphenamine and from 20,000 to 40,000 doses each of arsphenamine, sulfarsphenamine and tryparsamide. They found that reactions occurred at the rate of approximately 1 : 1,000 injections for all the drugs but tryparsamide; with this drug there were only 2 reactions for 39,602 injections. The death rate was 1 per 37,101 injections for arsphenamine and 1 per 26,162 injections for neoarsphenamine.

Arsphenamine Dermatitis.—Efforts to produce a phenomenon in experimental animals which is truly analogous to arsphenamine dermatitis in human beings continue, but with little success. Cormia [98] was able to produce a local sensitivity in the skin of the guinea-pig by endodermal injections of neoarsphenamine. This area would react to the intravenous injection of any trivalent arsenical compound but not to a pentavalent compound. He [99] further discovered that the reaction is not increased by the administration of staphylococcus toxin. Landsteiner and Jacobs [100] report the production of anaphylactic shock in guinea-pigs with or without the production of localized dermatitis at the point of the sensitizing injection. Frei [101] makes the potentially important observation that guinea-pigs may not be sensitized to the arsphenamines before they are about 4 weeks old, during pregnancy or shortly thereafter.

Dennie and Miller [102] report on 2 patients in whom adynamic ileus occurred as a complication of severe exfoliative dermatitis, with death

97. Cook, S. S., and Wingo, E. H.: Toxic Effects of Arsenical Compounds as Administered in the United States Navy in 1935, with Special Reference to Arsenical Dermatitis, U. S. Nav. M. Bull. **34**:569 (Oct.) 1936.

98. Cormia, F. E.: Experimental Arsphenamine Dermatitis, Canad. M. A. J. **34**:272 (March) 1936.

99. Cormia, F. E.: Experimental Arsphenamine Dermatitis: Reaction to Arsphenamine in Normal Guinea Pigs and in Guinea Pigs Given Staphylococcus Toxin, Arch. Dermat. & Syph. **34**:107 (July) 1936.

100. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals with Simple Chemical Compounds: III. Anaphylaxis Induced by Arsphenamine, J. Exper. Med. **64**:717 (Nov.) 1936.

101. Frei, Wilhelm: Tierexperimenteller Beitrag zur Frage "Salvarsan und Säugling," Acta dermat.-venereol. **18**:396, 1937.

102. Dennie, C. C., and Miller, E. S.: Arsphenamine Dermatitis: Paralytic Ileus and Perforation of the Intestine After Treatment with Arsphenamine, Arch. Dermat. & Syph. **35**:591 (April) 1937.

in both instances. Muir [103] describes a patient in whom death occurred twenty-eight days after the third injection of arsphenamine. Three days after this injection toxic erythema developed which subsided, and thirteen days after the injection a bullous eruption developed which persisted. Autopsy revealed generalized toxic degeneration of the vital organs.

Tarras-Wahlberg [104] demonstrates that the histamine content of the blood is increased during arsphenamine dermatitis and varies directly with the severity of the dermatitis. McLachlan [105] enthusiastically advocates the use of calcium thiosulfate in the treatment of drug reactions of all sorts.

Erythema of the Ninth Day.—Gordon [106] reports 2 cases in which the condition was typical of Milian's erythema of the ninth day and discussed the differentiation of "E 9," as he calls it, from the more usual form of arsphenamine dermatitis. The former comes on almost always on the ninth or tenth day after the first treatment, it is a scarlatiniform or morbilliform eruption which covers the face, the patient is not seriously ill and the eruption subsides within a few days. Further treatment with arsenicals is not contraindicated. The genesis of the condition is unknown, but Wainstein and Smelov [107] point out that it has many features in common with serum sickness.

Tryparsamide Dermatitis.—Generalized dermatitis following the administration of tryparsamide is rare. Robinson,[108] however, reports on 1 patient who showed an ill defined generalized maculopapular eruption after tryparsamide therapy. The localized, so-called fixed exanthems are more commonly observed. Pillsbury [109] reports a unique

---

103. Muir, K. B.: Vesiculobullous Dermatitis Following Administration of Arsphenamine: Report of a Case, Arch. Dermat. & Syph. **35**:226 (Feb.) 1937.

104. Tarras-Wahlberg, B.: Blood-Histamine in Salvarsan-Dermatitis, Acta dermat.-venereol. **18**:284, 1937.

105. McLachlan, A. E. W.: Calcium Thiosulphate in the Treatment of the Complications of Arsphenamine and Bismuth Therapy in Syphilis, J. Chemotherapy **13**:127 (Jan.) 1937.

106. Gordon, H.: Erythema of the Ninth Day, Brit. J. Dermat. **48**:281 (June) 1936.

107. Wainstein, A., and Smelov, N.: Sur la question de la symptomatologie, de la pathogénie et de la thérapeutique des exanthèmes précoces arsénobenzoliques —"érythèmes du neuvième jour" de Milan, Ann. de dermat. et syph. **8**:215 (March) 1937.

108. Robinson, S. S.: Dermatitis Due to Tryparsamide, Arch. Dermat. & Syph. **34**:251 (Aug.) 1936.

109. Pillsbury, D. M.: Fixed Arsenical Eruption: Sensitivity to Tryparsamide at Sites of Pigmentation Following Dermatitis Due to Silver Arsphenamine, Arch. Dermat. & Syph. **34**:103 (July) 1936.

observation: In his patient a fixed reaction to tryparsamide developed in cutaneous areas which four years before had been the site of a reaction to silver arsphenamine.

Arsphenamine Jaundice.—In an exhaustive discussion Soffer [110] brings out that a clear understanding of the mechanism of postarsphenamine jaundice is no nearer today than it was two decades ago, with confusion in diagnosis constantly arising. A study of the records of 158 patients with the condition, however, allowed some general conclusions. Arsphenamine, he found, causes jaundice half again as frequently as neoarsphenamine, while the complication is rare after tryparsamide. The white race is almost three times more likely to have posttreatment jaundice than Negroes, but the stage of the disease or the phase of the treatment seems to bear no influence. In half of his patients jaundice developed within ten days after the last treatment; i. e., it was "early;" in the remainder it was "delayed." In a description of the clinical course of postarsphenamine jaundice Soffer emphasizes that the premonitory symptoms—malaise, nausea and sometimes vomiting—usually appear from four to eight days before icterus. Ten of his patients had acute yellow atrophy of the liver; the remainder recovered. Of these, 81 were subsequently given further arsenical treatment, with the development of a second attack of jaundice in 2. This presents no striking contrast to the gross incidence (0.87 per cent) of posttreatment jaundice in the group of patients from which his material was drawn.

From this same group of patients who had recovered from postarsphenamine jaundice Campbell and Soffer [111] selected 27 in whom, as far as possible, the existence of any other cause of hepatic damage could be eliminated. For these patients they performed a bilirubin excretion test for hepatic function from six months to fourteen years after the jaundice had subsided and at various periods in relation to treatment with arsenicals. Ten of the 27 patients showed definite retention of bilirubin, 8 were on the borderline and the test for the remaining 9 gave normal results. The authors point out that the retention of bilirubin in this series is not as great as that found with an identical technic by Soffer and Paulson [112] in patients who had recovered from catarrhal jaundice. In addition, these authors performed the same test on 12 patients who had received moderate or relatively large amounts of anti-

110. Soffer, L. J.: Postarsphenamine Jaundice, Am. J. Syph., Gonor. & Ven. Dis. **21**:309 (May) 1937.

111. Campbell, A. D., and Soffer, L. J.: The Results of the Bilirubin Test for Liver Function on Patients Recovered from Arsphenamine Jaundice, Am. J. Syph., Gonor. & Ven. Dis. **21**:420 (July) 1937.

112. Soffer, L. J., and Paulson, Moses: Residual Hepatic Damage in Catarrhal Jaundice as Determined by the Bilirubin Excretion Test, Arch. Int. Med. **53**:809 (June) 1934.

syphilitic therapy but who had never been jaundiced. Two of them were found to show an abnormal retention of bilirubin.

Asteriades [113] tested the urine for urobilinogen before each injection, a half hour afterward and sometimes at longer intervals for a group of 110 patients under regular treatment with arsphenamine. Transient and slight urobilinogenuria was found in 9 patients, but in no instance was there other evidence of damage to the liver.

Graffar [114] revives the arguments which favor the essential identity of postarsphenamine jaundice and catarrhal jaundice and reports the occurrence of posttreatment jaundice in 6 per cent of his series of 7,000 patients. This is much higher than the incidence reported by most observers.

Soffer [115] studied the physicochemical changes in the blood of dogs in which hepatic damage had been produced by massive doses of arsphenamine. He regularly found a striking hemoconcentration, marked acidosis, due to increase in the quantity of lactic acid in the blood, and a considerable decrease in the chloride content of the blood serum. Somewhat less regularly he observed an increase in the inorganic phosphorus, potassium and magnesium contents of the blood serum. All the animals manifested evidences of nitrogen retention, and in 4 of the 6 hypoglycemia developed. Wien,[116] working with mice, found that the mortality following a standard dose of neoarsphenamine was half again as great for those animals fed on grains as for those fed on bread and milk. Although he could find no difference in the glycogen content of the liver in the two groups of animals, this author feels sure that the conditions of carbohydrate metabolism determine the reaction of the body to the administration of arsenical drugs.

Tryparsamide Amblyopia.—Sloan and Woods [117] studied 16 patients who had visual disturbances after the administration of tryparsamide. In 15 of these the reaction was chronic in its development, but the remaining patient was blind three days after the first injection. The authors describe the characteristic defect in the visual fields, which is diagnostic of the condition, and emphasize that there is a marked tendency toward

113. Asteriades, M.: Untersuchungen auf Urobilinogenurie nach Salvarsaneinspritzungen, Dermat. Wchnschr. **103**:1121 (Aug. 15) 1936.

114. Graffar, M.: Contribution à l'étude des ictères survenant au cours du traitement arsenical, Presse méd. **45**:661 (May 1) 1937.

115. Soffer, L. J.: Blood Electrolyte Studies in Experimental Acute Liver Injury Produced by Arsphenamine in Dogs, Proc. Soc. Exper. Biol. & Med. **35**: 160 (Oct.) 1936.

116. Wien, R.: The Influence of Diet on the Toxicity of Mercurochrome and of Neoarsphenamine, Quart. J. Pharm. & Pharmacol. **9**:48 (Jan.-March) 1936.

117. Sloan, L. L., and Woods, A. C.: The Effect of Tryparsamide on the Eye: A Clinical Study of the Objective Ocular Reaction, Am. J. Syph., Gonor. & Ven. Dis. **20**:583 (Nov.) 1936.

recovery if use of the drug is promptly and permanently discontinued. They conclude that the use of the drug carries with it little danger of permanent visual damage provided the optic nerve is previously normal. Wagener [118] arrives at essentially the same conclusions, but he is not inclined rigidly to prohibit the use of tryparsamide for patients with disease of the optic nerve. Fine and Barkan [119] also found that pretryparsamide examination of the ocular fundi and visual fields and a careful follow-up during the first course and periodically thereafter effectively safeguard the patient from the development of severe or permanent visual loss.

Intolerance to Tryparsamide.—Schoch [120] describes 3 patients who presented an anomalous response to the administration of tryparsamide. Instead of producing the tonic effect which is so usually observed, treatment with the drug occasioned malaise, weakness, obvious impairment of the general state of being and loss of weight. All symptoms cleared up on suspension of treatment with the drug, only to reappear on its resumption. Miller and O'Donnell [121] describe a patient who manifested toward tryparsamide an intolerance which simulated true allergic sensitization. This persisted for at least three years, although the patient received the trivalent arsenicals without reaction.

Medical Shock.—In a report of 3 cases Weinberg [122] calls attention to a little known and imperfectly understood syndrome which is best known as medical shock. All 3 patients presented the typical clinical picture of shock, which in 2 had come on immediately and in the third a few hours after the intravenous injection of neoarsphenamine. The condition persisted for several days. There were nausea and vomiting, marked hemoconcentration, evidences of nitrogen retention and an elevation of temperature. All 3 patients, however, recovered.

Granulocytopenia.—Bock [123] describes a patient in whom severe granulocytopenia and necrotic pharyngitis developed after she received the eighth dose of neoarsphenamine. The notable feature is that eight

118. Wagener, Henry P.: The Effect of Tryparsamide on the Optic Nerve, Am. J. M. Sc. **193**:286 (Feb.) 1937.

119. Fine, M., and Barkan, H.: Prevention of Ocular Complications in Tryparsamide Therapy, Am. J. Ophth. **2**:45 (Jan.) 1937.

120. Schoch, A. G.: Intolerance to Tryparsamide, Am. J. Syph., Gonor. & Ven. Dis. **20**:408 (July) 1936.

121. Miller, J. K., and O'Donnell, H. J.: Sensitivity to Tryparsamide, Arch. Dermat. & Syph. **35**:264 (Feb.) 1937.

122. Weinberg, T.: Medical Shock Following Intravenous Therapy with Neoarsphenamine, Am. J. Syph., Gonor. & Ven. Dis. **21**:376 (July) 1937.

123. Bock, H. E.: Ueber einen bemerkenswerten Einzelfall symptomatischer Agranulocytose während einer Neosalvarsan-Bismogenol Kur, Med. Welt **9**:1629 (Nov. 9) 1935.

months later she tolerated the further administration of neoarsphenamine without event.

Purpura Haemorrhagica—Falconer and his collaborators [124] describe 2 patients in whom they had repeatedly produced purpura haemorrhagica by the administration of neoarphenamine and in which the administration of mapharsen caused no untoward results.

Hemorrhagic Encephalitis.—Cormia [125] reports a case of hemorrhagic encephalitis following the administration of neoarsphenamine to a woman who was 23 years old and in the fifth month of pregnancy. He reviewed the literature on the subject and found reports of 135 cases. Forty-six of these patients were women and 34 were pregnant. Searching for some common factor which might suggest the etiology of the reaction, Cormia noted that almost all these patients had received doses of 0.45 Gm. or more of neoarsphenamine. He concludes, therefore, that an overdose of arsenic is the chief factor in causing the syndrome and suggests that the maximum weekly dose of neoarsphenamine for pregnant women should not exceed 0.3 Gm. The speciousness of this reasoning is readily obvious.

Venous Spasm.—One of the few troublesome features of the use of mapharsen is the occasional development of spasm of the vein into which the drug is injected, with attendant pain and sometimes consequent thrombosis. Schoch [126] brings out that cold compresses along the course of the vein bring relief and help to prevent thromboses. Heat, however, aggravates the condition.

THE PROPHYLAXIS OF SYPHILIS

In a general discussion of prophylaxis in the control of syphilis Moore [127] brings out that the methods which may be applied fall into three groups: mechanical prophylaxis, chemical prophylaxis and chemotherapeutic prophylaxis. The first is best accomplished with the condom. Chemical prophylaxis should be performed at a prophylactic station under the direction of trained personnel. It consists in local cleansing and medication of the parts of the body which have been exposed. Chemotherapeutic prophylaxis is best accomplished by the regular injec-

124. Falconer, E. H.; Epstein, N. N., and Wever, G. K.: Purpura Haemorrhagica Following the Administration of Neoarsphenamine: The Reaction to Neoarsphenamine Compared with the Reaction to Mapharsen, Arch. Int. Med. **58**:495 (Sept.) 1936.

125. Cormia, F. E.: Haemorrhagic Encephalitis from Neoarsphenamine in Pregnancy, Canad. M. A. J. **35**:610 (Dec.) 1936.

126. Schoch, A. G.: Treatment of Venous Spasm Resulting from Injection of Mapharsen or Arsphenamine, Arch. Dermat. & Syph. **34**:1031 (Dec.) 1936.

127. Moore, J. E.: Prophylaxis in the Control of Syphilis, South. M. J. **30**:149 (Feb.) 1937.

tion of a bismuth compound, but the potentialities of acetarsone by mouth in this field should be further investigated.

Chemical Prophylaxis.—Hood [128] and Esquier [129] bring out that chemical prophylaxis as enforced on troops or seamen at a central station breaks down primarily because the prophylaxis is taken too long after the initial exposure. This point has been long recognized and may in a large measure be obviated by education.

Astwazaturow and Juschkow [130] tested the effect of a large number of chemical and biologic agents on the motility of a virulent strain of S. pallida. They discovered that a 1:2,000 solution of several mercury salts, 1 per cent phenol, ethyl alcohol of more than 60 per cent concentration, potassium soap lather and hydrogen peroxide are effective in destroying spirochetes. Sodium soap lather and eau de Cologne (perfumed spirit N. F.) are not. In general, throughout a large series of substances which they tested the spirochete was found to be susceptible to those which are acid in reaction and to be resistant to those which give an alkaline reaction.

Chemotherapeutic Prophylaxis.—In spite of the encouraging results reported by Sonnenberg [131] and others, as previously mentioned,[1] on the bismuth prophylaxis of syphilis in selected groups, especially prostitutes, the method has not gained favor. Rabut,[132] Lacassagne and Lebeuf [133] and Gaté and Cuilleret [134] present a symposium on the subject, in which they agree that the method is not practically applicable and that there are many theoretical objections to its use.

THE TREATMENT OF EARLY SYPHILIS

Methods.—Stokes and Usilton [135] subject the League of Nations investigation of the treatment of early syphilis, which was previously

128. Hood, A.: The Prevention of Venereal Disease with Special Reference to Preventive Ablution Centers, J. Roy. Army M. Corps **48**:390 (June) 1937.

129. Esquier, A.: Prevention of Syphilis, Bull. Soc. franç. de dermat. et syph. **43**:1173 (June) 1936.

130. Astwazaturow, K. R., and Juschkow, P. D.: Ueber die Standhaftigkeit der blassen Spirochäten, Acta dermat.-venereol. **17**:43, 1936.

131. Sonnenberg, E.: Neuf ans de traitement préventif bismuthique de la syphilis, Bull. Acad. de méd., Paris **114**:374 (Nov. 5) 1935.

132. Rabut, R.: A propos du traitement préventif de la syphilis, Bull. Soc. franç. de dermat. et syph. **43**:1186 (June) 1936.

133. Lacassagne, J., and Lebeuf, F.: Considérations sur la métallo-prévention chez les prostitutes, Bull. Soc. franç. de dermat. et syph. **43**:1189 (June) 1936.

134. Gaté, J., and Cuilleret, P.: A propos de la métallo-prévention par le bismuth, Bull. Soc. franç. de dermat. et syph. **43**:1191 (June) 1936.

135. Stokes, J. H., and Usilton, L. J.: Continuous and Intermittent Treatment for Early Syphilis: A Critical Review of the American and the League of Nations' Investigation, with Additional Evaluations, Arch. Dermat. & Syph. **35**:377 (March) 1937.

reviewed,[1a] to a critical resurvey and bring out some interesting additional information. They find that Martenstein's [136] report actually allows no critical comparison between the results obtained by continuous and those obtained by intermittent treatment. This is because of the fact that while patients were counted as having had continuous treatment only if they actually had been so treated, many patients were considered as having had intermittent treatment when the treatment really had been haphazard. These authors therefore went over the material of the Cooperative Clinical Group and discovered that whereas no difference between the two methods could be demonstrated during the first three months of treatment, after that period had passed the system of continuous treatment could be shown to produce significantly better results, with no more reactions. Sixty-eight per cent of the group of patients who had received continuous treatment had attained a negative reaction to serologic tests for syphilis at the end of a year. In the group who had only a month's rest from treatment during the first year, however, only 40 per cent had been so fortunate.

Moore [137] recapitulates the evidence which favors the continuous method of treatment and brings out that the proper treatment of patients with early syphilis is of importance not only to the patient and the public health but also to the public expense. This is because it is much cheaper to treat a patient for early syphilis than to care for him when he is broken down with late lesions of the disease. By and large, however, patients with early syphilis are not being properly treated. The reason for this lies, he says, in part within the biology of the disease, with its high incidence of symptomless infection, in part with the laity and in part with physicians. The fault which lies with the laity is ignorance and, worse, unwillingness to learn. The fault of the physicians is threefold: They have not taken the lead in education of the laity, they do not apply modern methods for early diagnosis and, though adequate methods of treatment have been developed, they do not apply them.

Rosahn [138] and an editorial commentator [139] deplore the abandonment of tried methods of treatment of early syphilis for the untried methods of fever therapy or of treatment with drugs administered by mouth.

136. Martenstein, cited by Padget and Moore.[1b]

137. Moore, J. E.: The Continuous Method of Treatment of Early Syphilis, Ann. Int. Med. **10**:30 (July) 1936.

138. Rosahn, P. D.: The Treatment of Syphilis: Modern Methods Versus Artificial Fever and Orally Administered Bismuth Preparations, J. Chemotherapy **13**:49 (July) 1936.

139. The Oral Medication of Syphilis, editorial, Am. J. Syph., Gonor. & Ven. Dis. **21**:456 (July) 1937.

The former topic was made the subject of extensive comment in a previous review;[1b] to this Rosahn adds the weight of another opinion. Concerning the treatment of syphilis by oral medication the editorial comment concludes:

> It is felt by many that there is little place at present for new drugs in the treatment of syphilis unless they show promise of superiority to the most efficient of those in use at the present time. This does not mean that efforts to evolve new preparations, whereby the treatment of syphilis would become shorter, less expensive, and more convenient, should not continue. However, before any preparation is offered for general use in the treatment of syphilis, no matter how it is to be administered, it must be preceded by the same careful experimental and clinical study which preceded the introduction of arsphenamine. There is insufficient evidence that the drugs proposed for the oral treatment of syphilis have met these requirements.

Results.—In addition to the results of the studies by the Cooperative Clinical Group and the Health Organization of the League of Nations which have been previously discussed,[1b] there now is accumulating an impressive body of independently conducted studies which seek even more detailed and comprehensive evaluation of the results of the treatment of patients with early syphilis. Milian and his collaborators[140] were able in 1935 to follow 375 of the patients with early syphilis who had been treated at the St. Louis Dispensary between 1922 and 1924, thus giving a ten year follow-up period. All these patients had received treatment which would be considered minimal by the standards of the Cooperative Clinical Group. Of the 375 patients, 29.8 per cent had had a recurrence or relapse, but 243, or 64.8 per cent, were apparently well at the end of ten years. After a shorter follow-up period Nicastro[141] found that among 875 patients who had been treated at Palermo during the past five years the incidence of late syphilis was strictly related to the amount of treatment which the patient had had for early syphilis.

In a unique study Rosahn[142] investigated the effect of inadequate treatment of patients with early syphilis on the final outcome of the disease process. His study is based on the data for 409 patients who had received less than 20 injections of an arsphenamine preparation and of heavy metal within a year during the first two years after the onset of the disease. He was able to demonstrate the superiority of continuous over intermittent or irregular treatment and to show that there was a relation between the amount of treatment which the patient had received and the eventual result. In this group there were 134 (32.8

140. Milian, G.; Périn, L., and Lafourcade: Résultats éloignés du traitement de la syphilis, Rev. franç. de dermat. et de vénéréol. **12**:511 (Nov.) 1936.

141. Nicastro, A.: La sorte lontana dei sifilitici in rapporto alle cure iniziali, Gior. ital. di dermat. e sif. **76**:1477 (Dec.) 1935.

142. Rosahn, P. D.: The Inadequate Treatment of Early Syphilis, Am. J. M. Sc. **193**:534 (April) 1937.

per cent), most of whom were observed more than two years after the cessation of treatment for whom the result of treatment was classified as satisfactory. The author points out, however, that whereas a normal cerebrospinal fluid presents to these patients a virtual guarantee against the subsequent development of neurosyphilis, they face an unknown and unmeasurable hazard in the form of the later development of cardiovascular syphilis.

CLINICAL PHENOMENA IN EARLY SYPHILIS

Extragenital Primary Syphilis.—The large number of patients with late syphilis who are able to give no history suggesting the noting of a genital primary lesion provides a constant stimulus for interest in the incidence of extragenital infection. It is axiomatic that many, perhaps a majority, of the extragenital primary lesions go unrecognized, but a study such as that of Schmidt [143] serves as a reminder that primary syphilis may occur, as Stokes says, anywhere but on the teeth and nails. During the ten year period ending in 1935 this author observed 305 men and 66 women with primary syphilis, which was extragenital in localization in 6.5 per cent of the former and in 15.5 per cent of the latter. The majority of the extragenital lesions were about the mouth, with the tonsil the most common site.

Reports of individual cases confirm the ubiquity of primary syphilis. Perkins [144] and Fox [145] describe the case of an 18 year old girl who had a chancre of the bulbar conjunctiva. The mode of infection was not clear. Weissenbach and his collaborators [146] report the occurrence of a chancre in the right nostril.

The Diagnosis of Early Syphilis.—Photinos [147] observes that the diagnosis of seronegative primary syphilis by dark field examination may be greatly impeded by the inaccessibility of the lesion under suspicion, by the fact that the patient has applied to it spirocheticidal medication or by the fact that it is so old that organisms have disappeared from the surface. He recommends therefore the dark field examination of material obtained by gland puncture as a routine procedure and

143. Schmidt, W.: Statistisch-klinische Betrachtungen über die von 1926 bis 1935 beobachteten Erkrankungen an Lues I und Lues II, Dermat. Ztschr. **73**:285 (June) 1936.

144. Perkins, O. P.: Chancre of the Conjunctiva: Report of a Case, Arch. Ophth. **17**:381 (Feb.) 1937.

145. Fox, H.: Chancre of the Bulbar Conjunctiva, Arch. Dermat. & Syph. **35**:553 (March) 1937.

146. Weissenbach, Basch and Le Baron: Chancre syphilitique fissuraire de la narine, Bull. Soc. franç. de dermat. et syph. **43**:1259 (June) 1936.

147. Photinos, P.: La recherche du tréponème par la ponction des ganglions méthode de Hoffmann modifiée par Gougerot, Ann. d. mal. vén. **31**:481 (July) 1936.

reports the impressive results of his own experience. No patient for whom gland puncture gave negative results subsequently was proved to have had primary syphilis. There were in his series 104 patients for whom gland puncture gave positive results. In 36 of these patients spirochetes could be demonstrated in material from the primary lesion. For 46 of the remaining 68, for whom dark field examination of material from the suspected primary lesion could not be carried out for technical reasons or for whom negative results were obtained, the serologic test for syphilis gave a positive reaction. For the remaining 22, or 21 per cent of the entire group, however, the diagnosis of seronegative primary syphilis was made by gland puncture alone.

Carley [148] brings up again the rôle of gonorrhea in masking the lesions of early syphilis when the two diseases coexist. From the clinic of the United States Public Health Service in Hot Springs, Ark., he was able, by routine serologic follow-up of patients with gonorrhea, to detect 8 fresh infections with syphilis. Unfortunately, he does not indicate the total number of patients who were followed in this study.

TRANSFUSION SYPHILIS

No one pretends that the transmission of syphilis by the transfusion of blood is ever to be justified. Until the immediate past, however, those who had participated in or were aware of an instance of this regrettable tragedy were so secretive that the medical literature contains no reliable estimate either of the incidence of transfusion syphilis or of the variety of human error most frequently responsible for its production. More recently observers have become bolder: Willis [149] reports the instance of a woman who acquired syphilis from a donor who was known to have syphilis. Because he had had 6 intravenous treatments and had manifested a negative reaction to a serologic test for syphilis, he was thought to be a safe donor. In the recipient, however, syphilis developed. Tasaki [150] reports a similar case.

Gilman [151] presents an exhaustive discussion of the subject. He points out that careful examination of donors is desirable but that if a choice must be made between an unknown donor and one known to have late syphilis, the latter is probably safer.

---

148. Carley, P. S.: Infection with Syphilis Masked by Gonorrhea, Ven. Dis. Inform. **18**:21 (Feb.) 1937.

149. Willis, M. W.: Transfusion Syphilis, New York State J. Med. **37**:60 (Jan.) 1937.

150. Tasaki, K.: Syphilis Transmitted by Blood Transfusion, J. Orient. Med. **25**:54 (Sept.) 1936.

151. Gilman, R. L.: Syphilis and Transfusion, Indian J. Ven. Dis. **2**:176 (Sept.) 1936.

REINFECTION WITH SYPHILIS

Reinfection with syphilis is troublesome to prove. It does occur, however, and Millspaugh [152] reports 18 instances which he discovered among the 252 records of cases of syphilis on file at the Naval Air Station in Pensacola, Fla. This author was impressed primarily by the significance of reinfection as signaling the biologic "cure" of the first infection, and carefully quantitated the amount of treatment which each patient had received for the first infection. He found that on the average each man had received 27.7 injections of neoarsphenamine, 16.2 injections of a bismuth compound and 10 injections and 31.1 inunctions of mercury.

Attilio [153] reports a single case of reinfection which seems beyond cavil, and Sézary [154] describes a patient who clearly seems to have sustained three infections with syphilis.

LATE SYPHILIS

Most of the recent literature on late syphilis consists of reports of individual cases or of small groups. Only a few of these are of sufficient interest to warrant inclusion here. Among the more general discussions, da Silva Mello [155] presents an unconvincing and completely undocumented attempt to define chronic syphilitic nephritis.

McNamara [156] and White and Gaines [157] discuss syphilitic orchitis in the course of general considerations of the causes for testicular swelling. Both emphasize the necessity for the greatest care in the differential diagnosis between syphilis, tuberculosis and malignant disease. Keyes [158] reports the case of a man 60 years of age who was known to have syphilis and from whom a prostatic mass was removed. Microscopic study showed that it might well be gummatous.

---

152. Millspaugh, J. O.: An Analysis of Eighteen Syphilitic Reinfections, U. S. Nav. M. Bull. **35**:240 (April) 1937.

153. Attilio, A.: Un caso di presumibile reinfezione sifilitica, Gior. ital. di dermat. e sif. **77**:751 (Oct.) 1936.

154. Sézary, A.: Trois contaminations syphilitiques chez un même sujet en 12 ans, Bull. Soc. franç. de dermat. et syph. **44**:349 (Feb.) 1937.

155. da Silva Mello, A.: Die chronischen syphilitischen Nephritiden als eine selbständige Gruppe von Nierenkrankheiten, Deutsche med. Wchnschr. **62**:70 (Jan. 10) 1936.

156. McNamara, E. P.: Syphilis, Tuberculosis and Malignant Tumors of Testis: Pathology and Differential Diagnosis, J. Iowa M. Soc. **27**:28 (Jan.) 1937.

157. White, E. W., and Gaines, R. B.: The Clinical Significance and Rationale of Management of Testicular Swellings, J. A. M. A. **108**:1227 (April 10) 1937.

158. Keyes, E. L.: Granuloma of the Prostate Possibly Due to Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:418 (Oct.) 1936.

The most dramatic case of the year is reported by Wilhelm and Scholtz.[159] These authors supply postmortem photographs which show an unbelievably extensive ulceration, with destruction of tissue about the head, neck and upper portion of the body. The process had been developing for four years from an original lesion in the mouth. Fortunately, the authors were able to recover S. pallida from the lesion. The illustrations must be seen to be appreciated.

Syphilis of the Stomach.—Carter,[160] in a general discussion of the roentgenologic diagnosis of gastric syphilis, brings out the characteristics which warrant a therapeutic test for syphilis before the institution of more radical measures. The most important of these are, in a patient with syphilis, the presence of an annular prepyloric constriction in the absence of a palpable mass, absence of peristalsis but some flexibility on manipulation, and minor symptoms. Widén[161] and Fenster[162] report individual cases in which the diagnosis of syphilis of the stomach was carefully established. Rentschler[163] reports that 1 of a group of 100 patients with surgical conditions of the stomach had gastric syphilis with duodenal obstruction.

CARDIOVASCULAR SYPHILIS

Incidence of Cardiovascular Syphilis.—Among a group of 485 seamen with heart disease Arenberg[164] found that 130 (27 per cent) had syphilis and that 57 (12 per cent) were suffering from outspoken cardiovascular syphilis.

From a study of necropsy records Nickel[165] found that some lesion of syphilis had been recorded for 1,203 (6 per cent) of the 20,040 patients examined post mortem in Dusseldorf from 1907 through 1933. In the first period, 1907 through 1915, 75 per cent of the patients with anatomically demonstrable lesions of syphilis manifested syphilis of the aorta. During the next decade the observed incidence of aortic involve-

159. Wilhelm, L. F. X., and Scholtz, J. R.: Extensive Ulcerations in Wholly Untreated Syphilis, Arch. Dermat. & Syph. **34**:242 (Aug.) 1936.

160. Carter, R. A.: Non-Carcinomatous Tumors of the Stomach, Radiology **28**:301 (March) 1937.

161. Widén, A.: A Case of Visceral Syphilis Operated upon Twice—with an Interval of Twenty-Six Years—Because of Suspected Cancer of the Stomach, Acta dermat.-venereol. **18**:216, 1937.

162. Fenster, E.: Syphilitischer Schrumpfmagen, Arch. f. klin. Chir. **187**:705 (Jan. 25) 1937.

163. Rentschler, C. B.: Surgical Lesions of the Stomach: Immediate and Late Results in One Hundred Consecutive Cases, Am. J. Surg. **35**:529 (March) 1937.

164. Arenberg, H.: Heart Disease Among Seamen, Am. Heart. J. **13**:197 (Feb.) 1937.

165. Nickel, H.: Statistische Untersuchungen über die Häufigkeit der Lues am Obduktionsmaterial, Klin. Wchnschr. **15**:121 (Jan. 25) 1936.

ment rose to 85 per cent of the group with syphilitic lesions, and in the period from 1926 through 1933, it rose again to 89 per cent. It must be emphasized, however, that these figures deal with the incidence of aortic involvement in patients with some lesion of syphilis, aortic or otherwise, which could be observed at necropsy. There is sad need for similar studies of all patients for whom a clinical diagnosis of syphilis has been made, especially those with latent syphilis who have died from other causes.

In a group of 200 Negroes with sufficiently severe forms of neurosyphilis to require institutionalization, Tildon [166] found that 38 had serious syphilitic disease of the cardiovascular system and that 27 others were suffering from other serious cardiovascular disorders. Cole and his colleagues [167] discovered that 10 per cent of the 6,253 patients with late syphilis included in the study made by the Cooperative Clinical Group manifested cardiovascular syphilis either when first seen or subsequently.

The Diagnosis of Cardiovascular Syphilis.—Kemp and Cochems [168] had the unique opportunity to study posterior-anterior teleroentgenograms which had been made by an identical technic for 600 nonsyphilitic persons and 1,000 patients with syphilis. The former represented a fair sample of the population; the latter group was not weighted in either direction, since the incidence of cardiovascular syphilis was essentially the same (12.7 per cent) [169] as that noted by others who have studied large groups of patients with syphilis. The teleroentgenograms were all remeasured according to the method of Vaquez and Bordet, and the clinical record of each patient was searched for relevant data. They found:

2. The increased widening of the supracardiac shadow resulting from essential hypertension and arteriosclerosis with or without hypertension was the same in nonsyphilitic as in syphilitic individuals without syphilitic heart disease.

3. The increase in the width of the aortic arch shadow as a result of advancing age was the same in both syphilitic and nonsyphilitic individuals without heart disease.

166. Tildon, T. T.: Cardiovascular Disease Complicating Neurosyphilis Among Negro Veterans, M. Bull. Vet. Admin. **13**:144 (Oct.) 1936.

167. Cole, H. N.; Usilton, L. J.; Moore, J. E.; O'Leary, P. A.; Stokes, J. H.; Wile, U. J.; Parran, T., Jr., and McMullen, John: Cooperative Clinical Studies in the Treatment of Syphilis: The Effect of Specific Therapy on the Prophylaxis and Progress of Cardiovascular Syphilis J. A. M. A. **108**:1861 (May 29) 1937.

168. Kemp, J. E., and Cochems, K. D.: Studies in Cardiovascular Syphilis: I. Teleroentgenography in the Diagnosis of Early Syphilitic Aortitis; a Comparison of Findings in One Thousand Syphilitic and Six Hundred Nonsyphilitic Individuals, Am. Heart J. **13**:297 (March) 1937.

169. Cochems, K. D., and Kemp, J. E.: Studies in Cardiovascular Syphilis: II. The Incidence of Syphilitic Aortitis; a Study of One Thousand Syphilitic Individuals, Am. J. Syph., Gonor. & Ven. Dis. **21**:282 (May) 1937.

4. Only 59 per cent of the patients with clinically recognizable syphilitic aortitis showed teleroentgenographic evidence of aortic dilatation.

The authors therefore conclude that there is no evidence that the diagnosis of uncomplicated syphilitic aortitis can be made by teleroentgenography alone. Fluoroscopy and careful clinical evaluation of symptoms and physical signs are essential.

In a second communication these authors [169] report the distribution of the incidence of cardiovascular syphilis in their group of 1,000 syphilitic patients. The gross incidence of cardiovascular syphilis was 12.7 per cent, but it was 10.8 per cent for the women and 13.4 per cent for the men. These figures, they point out, are in essential agreement with the findings of Bruusgaard and of Turner. They are, however, sharply in contrast with the findings reported by Maynard and his colleagues,[170] who discovered cardiovascular syphilis in 41.9 per cent of a group of 346 persons with syphilis. This difference, Kemp and Cochems think, is unquestionably due to differences in the criteria for the diagnosis of early syphilitic aortitis which were employed. They made the diagnosis of uncomplicated aortitis only on the demonstration of at least three diagnostic criteria, whereas Maynard and his group made the diagnosis solely by the teleroentgenographic demonstration of "increased aortic width."

Padget and Moore [171] reviewed the literature regarding roentgenologic methods in the diagnosis of uncomplicated syphilitic aortitis and conclude:

> From examination of the evidence it seems clear that teleroentgenography in the posteroanterior position offers no reliable aid toward the early diagnosis of uncomplicated syphilitic aortitis, and the usefulness of other methods of examination is far from established. The studies of various workers, particularly Fray, regarding the use of the left anterior oblique position for teleroentgenography, preceded and supplemented by fluoroscopy, seem the most promising and should be further elaborated, and the roentgenologic findings should be closely compared with clinical and necropsy data. The preferable method of investigation would be by serial roentgenographic studies of groups of normal and diseased individuals, at periodic intervals over a lifetime, ending with necropsy confirmation of the presence or absence of aortic disease.

From a study of large numbers of roentgenokymograms Scott and his co-workers [172] conclude that aortic regurgitation produces a perfectly

170. Maynard, E. P., Jr.; Curran, J. A.; Rosen, I. T.; Williamson, C. G., and Lingg, C.: Cardiovascular Syphilis: Early Diagnosis and Clinical Course of Aortitis in Three Hundred and Forty-Six Cases of Syphilis, Arch. Int. Med. **55**:873 (June) 1935.

171. Padget, P., and Moore, J. E.: The Roentgenologic Diagnosis of Syphilitic Aortitis, Am. J. Syph., Gonor. & Ven. Dis. **21**:199 (March) 1937.

172. Scott, W. G., and Moore, S.: Roentgenokymography: Its Clinical and Physiological Value in the Study of Heart Disease, Ann. Int. Med. **10**:306 (Sept.) 1936. Scott, W. G.; Moore, S., and McCordock, H. A.: Roentgenkymographic Studies of Cardiac Conditions, Radiology **28**:196 (Feb.) 1937.

diagnostic roentgenokymographic tracing. Characteristic changes were found, however, in only about half of a group of patients whose condition had been diagnosed clinically as uncomplicated syphilitic aortitis. These changes, too, were indistinguishable from those seen in patients with arteriosclerosis. The picture produced by aneurysm of the aorta was found to be even less distinctive.

The Rôle of Occupation in the Genesis of Cardiovascular Syphilis.—Cochems and Kemp [173] investigated the relation between occupation and incidence of cardiovascular syphilis in the 749 men among the 1,000 patients with syphilis who had been dealt with in other studies.[174] They found the incidence of syphilitic aortic disease to be greater among persons of intermediate and heavy occupational pursuits (14.1 per cent) than among those who followed sedentary occupations (8.7 per cent). The incidence of uncomplicated aortitis, however, was greater among persons who followed the lighter occupations, whereas aneurysm and aortic regurgitation occurred much more commonly among those who followed occupations which demanded a certain amount of physical exertion.

General Considerations.—Willius [175] and Goeckerman and Wilhelm [176] present general discussions of the problems of cardiovascular syphilis, the latter placing particular emphasis on the practical aspects of management of the patient.

Bruenn, Turner and Levy [177] correlate the clinical cardiac symptoms and autopsy observations for 476 patients, 64 of whom had syphilitic aortitis. Pain had not been noted by any of the patients who did not manifest encroachment on the coronary ostia. They conclude, therefore, that pain is not a part of the picture of uncomplicated aortitis.

Andersen and McCutchan [178] reiterate the observation that disturbance of cardiac rhythm is rare in patients with cardiovascular syphilis.

---

173. Cochems, K. D., and Kemp, J. E.: Studies in Cardiovascular Syphilis: III. The Effect of Occupation upon the Incidence and Type of Syphilitic Aortitis, Am. J. Syph., Gonor. & Ven. Dis. **21**:408 (July) 1937.

174. Kemp and Cochems.[168] Cochems and Kemp.[169]

175. Willius, F. A.: Cardiovascular Syphilis, Mississippi Doctor **15**:1 (June) 1937.

176. Goeckerman, W. H., and Wilhelm, L. F. X.: Cardiovascular Syphilis, with Special Reference to Its Practical Management, Am. J. Syph., Gonor. & Ven. Dis. **20**:412 (July) 1936.

177. Bruenn, H. G.; Turner, K. B., and Levy, R. L.: Notes on Cardiac Pain and Coronary Disease: Correlation of Observations Made During Life with Structural Changes Found at Autopsy in Four Hundred and Seventy-Six Cases, Am. Heart J. **11**:34 (Jan.) 1936.

178. Andersen, M. C., and McCutchan, G. R.: One Thousand Patients with Heart Tracings, Nebraska M. J. **21**:128 (April) 1936.

Syphilitic Myocarditis.—Norris [179] has long maintained that syphilis attacks the myocardium much more frequently than is generally conceded. The failure to demonstrate spirochetes in the myocardium does not, he says, necessarily imply that they are absent. In his opinion myocardial syphilis should be suspected in any patient with early syphilis who presents cardiac complaints, and he feels that it would be a great step forward if physicians would worry more about the heart and less about the chancre of patients with early syphilis. He describes 3 patients, 1 with associated aortic regurgitation, who died of myocardial failure. In each case Weller was able to demonstrate spirochetes in the myocardium.

Reifenstein [180] reviews the literature on syphilitic myocarditis which has accumulated since 1918 and reports a case. His patient was a white man 26 years of age who had had syphilis for seven years. Three months before the final illness a cutaneous eruption, similar to one which he had noted two years after the original infection, appeared. Treatment for syphilis was begun but was abandoned two weeks before the acute illness began. He presented the clinical picture of acute myocardial infarction and a papulosquamous eruption, the nature of which was not clear. Death occurred seventeen days after the onset, and necropsy revealed acute granulomatous myocarditis with multiple caseating foci. These were histologically typical of gumma.

Taussig and Oppenheimer [181] report a somewhat similar instance in a child 6 years of age who had sickle cell anemia and tuberculosis and who had acquired syphilis by transfusion. Recurrent secondary syphilis developed two or three days after the ninth dose of sulfarsphenamine, and the child died within two weeks of cardiac failure. Necropsy revealed granulomatous myocarditis the appearance of which was compatible with a diagnosis of gumma.

Syphilitic Aortitis and Bacterial Endocarditis.—In reviewing the records of 193 cases of bacterial endocarditis Smith [182] found 3 in which there had been coexistent syphilitic aortitis. Two were from the group of 22 cases in which the condition was classified as acute bacterial endocarditis; the third was found among the 171 cases in which the disease had been of the more usual subacute variety.

179. Norris, J. C.: Syphilis of the Myocardium and Coronary Arteries, J. A. M. A. **108**:169 (Jan. 16) 1937.

180. Reifenstein, E. C.: Acute Gummatous Myocarditis Simulating Acute Myocardial Infarction, Ann. Int. Med. **10**:241 (Aug.) 1936.

181. Taussig, H. B., and Oppenheimer, E. H.: Severe Myocarditis of Unknown Etiology, Bull. Johns Hopkins Hosp. **59**:155 (Sept.) 1936.

182. Smith, F. J.: The Co-Existence of Syphilis of the Aorta and Bacterial Endocarditis, Internat. Clin. **2**:1, 1937.

The Effect of Treatment on the Histologic Appearance of Syphilitic Aortitis.—Hood and Mohr [183] compared the microscopic pathologic appearance of the aorta in two groups each of 17 patients. The patients of one group were known to have received at least the equivalent of eight months of continuous antisyphilitic therapy. The second group was made up of patients known to have received no antisyphilitic treatment. The only differences observed in the microscopic appearance of the aorta were relatable to the duration of the syphilitic infection; in smaller groups in which age and duration of infection were strictly comparable, the histologic pictures of the aortic wall were practically identical, whether the patient had received treatment or not.

Dissecting Aneurysm.—Sherman [184] presents a monumental contribution on dissecting aneurysm, which is based on a study of 300 cases. Seventeen of these he had personally observed; the remainder had been reported on in the literature. He says:

> Syphilitic mesaortitis was present in my case No. 2 (F, 39). This is unusual, as absence of frankly syphilitic disease of the aorta is generally regarded as one of the outstanding differences between ordinary aneurysm and dissecting aneurysm. But in 12 others of the reported cases syphilis was deemed to be present . . . Further, in 8 case reports there are . . . suggestive descriptions, but no microscopic examination . . . (He concludes therefore that) ordinarily syphilis is not a prominent factor in the aetiology of dissecting aneurysms.

Glendy, Castleman and White [185] arrive at the same conclusions from a study of the literature and of their 19 cases. Contrariwise, Peery [186] feels that 1 of his 5 patients certainly and another probably were syphilitic. He points out, however, that even if a patient has syphilis, the usual factors must operate before a dissecting aneurysm can form.

Intracranial Aneurysm.—Dial and Maurer [187] report that in only 2 of their group of 13 patients with intracranial aneurysm was syphilis the responsible factor. In 1 of these there were multiple syphilitic aneurysms of the right middle cerebral artery; the other had syphilitic aneurysms of both internal carotid arteries.

---

183. Hood, B. J., and Mohr, C. F.: The Microscopic Pathologic Appearance of the Aorta in Treated and Untreated Patients with Syphilitic Aortitis, Am. J. Syph., Gonor. & Ven. Dis. **21**:177 (March) 1937.

184. Sherman, T.: Dissecting Aneurysms, Medical Research Council, Special Report Series, no. 193, London, His Majesty's Stationery Office, 1934.

185. Glendy, R. E.; Castleman, B., and White, P. D.: Dissecting Aneurysm of the Aorta: A Clinical and Anatomical Analysis of Nineteen Cases (Thirteen Acute), with Notes on the Differential Diagnosis, Am. Heart J. **13**:129 (Feb.) 1937.

186. Peery, T. M.: Dissecting Aneurysm of the Aorta, with a Report of Five Cases, Am. Heart J. **12**:650 (Dec.) 1936.

187. Dial, D. L., and Maurer, G. B.: Intracranial Aneurysms: Report of Thirteen Cases, Am. J. Surg. **35**:2 (Jan.) 1937.

NEUROSYPHILIS

Incidence of Neurosyphilis.—Matras [188] examined the cerebrospinal fluid of 721 patients with early syphilis before the institution of treatment. In 95 instances (13 per cent) a positive result was obtained. The degree of abnormality was striking, however, only in patients with secondary syphilis.

In two studies from the Boston Psychopathic Hospital Moore and Merritt [189] discuss the rôle played by neurosyphilis in the production of mental disease. They found that when corrections were made for the number of patients found to be "not psychotic" and for the number of patients readmitted syphilis of the nervous system was responsible for the mental disease in 9.3 per cent of their patients. In 94 per cent of this group the neurosyphilitic disease was dementia paralytica.

In the course of the routine postmortem examination of the cranial contents of 5,150 patients Peers [190] reports that one hundred and eighty-eight tumors of the central nervous system were discovered. Three were gummas.

The Genesis of Neurosyphilis.—The studies of the Cooperative Clinical Group, with O'Leary [191] as spokesman, clearly show the effect of discontinuity of treatment in promoting the development of involvement of the neuraxis. Of the group of patients who had received an adequate amount of treatment for early syphilis, neurosyphilis occurred in only 7.5 per cent of those whose treatment had been continuous but in 22.6 per cent of the group of patients who had received treatment irregularly.

Wile and his co-workers [192] show that as for neurosyphilis in general the absence or inadequacy of treatment of early syphilis is a predominant factor in the precocious development of dementia paralytica and tabes dorsalis.

---

188. Matras, A.: Zur Frage des positiven Liquors im 1. Jahre der Syphilis, Arch. f. Dermat. u. Syph. **175**:85 (Jan. 2) 1937.

189. Moore, M., and Merritt, H. H.: Dementia Paralytica at the Boston Psychopathic Hospital, New England J. Med. **215**:108 (July 16) 1936; Rôle of Syphilis of Nervous System in Production of Mental Disease: Survey of Various Forms of Neurosyphilis Occurring at Boston Psychopathic Hospital from 1912 to 1934, J. A. M. A. **107**:1292 (Oct. 17) 1936.

190. Peers, J. H.: The Occurrence of Tumors of the Central Nervous System in Routine Autopsies, Am. J. Path. **12**:911 (Nov.) 1936.

191. O'Leary, P. A., and others: Cooperative Clinical Study in the Treatment of Syphilis: Asymptomatic Neurosyphilis, Arch. Dermat. & Syph. **35**:387 (March) 1937.

192. Wile, U. J.; Poth, D. O., and Barney, B. F.: Dementia Paralytica and Tabes: A Study with Reference to Precocious Development, J. A. M. A. **105**:1329 (Oct. 26) 1935.

As the result of an anthropometric investigation of 27 patients with dementia paralytica, Guirdham [193] concludes that no single body type exists in this group.

Nonne [194] considers the genesis of neurosyphilis at some length and expresses the opinion that treatment of early syphilis has little or nothing to do with the prevention or encouragement of the subsequent development of neurosyphilis except hasten its onset. The entire matter, he says, is to be summed up in Ricord's statement: "Each individual has his own [kind of] syphilis."

As an argument for the existence of a neurotropic strain of S. pallida, Jörimann [195] presents the instance of marital partners in both of whom tabes dorsalis developed.

Merritt, Putnam and Campbell [196] compared the histologic picture of the brains of patients who had died of dementia paralytica with anatomic changes which by experimental maneuvers they were able to produce in the cerebral cortical substance of dogs. From this experience they suggest that the degenerative changes in the cortex in dementia paralytica may be regarded as secondary to anoxemia produced by endarteritis of small cortical vessels.

Syphilitic Epilepsy.—Bruetsch and Bahr [197] clearly differentiate between convulsions occurring in patients with neurosyphilis and true idiopathic epilepsy. The term syphilitic epilepsy is used only for neurosyphilis associated with convulsive seizures which resemble idiopathic epilepsy in all respects and which leave no signs of organic disease of the brain. Clinically, differentiation from true idiopathic epilepsy is difficult and sometimes impossible. The condition is rare, but cases have been reported by reliable observers. To this small group the present authors add a full clinical and pathologic description of 5 cases.

General Clinical Considerations.—Winkelman [198] brings to completion his exhaustive monographic discussion of syphilitic diseases of the

193. Guirdham, A.: The Body Type of the General Paralytic, J. Neurol. & Psychopath. **16**:363 (April) 1936.

194. Nonne, M.: Erinnerungen und Bekentnisse auf dem Gebiet der Neurolues, Deutsche Ztschr. f. Chir. **248**:177 (Dec.) 1936.

195. Jörimann, A.: Conjugale Tabes mit ähnlichen klinischen Symptomen, Schweiz. med. Wchnschr. **67**:226 (March 13) 1937.

196. Merritt, H. H.; Putnam, R. J., and Campbell, A. C. P.: Pathogenesis of Cortical Atrophy Observed in Dementia Paralytica, Arch. Neurol. & Psychiat. **37**:85 (Jan.) 1937.

197. Bruetsch, W. L., and Bahr, M. A.: Syphilitic Epilepsy, Am. J. Syph., Gonor. & Ven. Dis. **21**:255 (May) 1937.

198. Winkelman, N. W.: Syphilis of the Spinal Cord, Am. J. Syph., Gonor. & Ven. Dis. **20**:421 (July) 1936.

spinal cord. Langworthy and his co-workers [199] assemble the results of their earlier contributions, previously reviewed,[1b] regarding the effect of the lesions of tabes dorsalis on the control of micturition. Rubritius [200] presents the results of similar studies, with similar conclusions. Muschet [201] particularly emphasizes the value of repeated cystometric examination of patients with disturbance of the neurologic control of micturition to determine whether progress, arrest or improvement is taking place.

Bujadoux and Gourevitch [202] have devised a rather complicated apparatus for detecting the presence of ataxia of the pupil to a measured light stimulus before the development of a true Argyll Robertson phenomenon. The method, they say, is of great value in the early diagnosis of neurosyphilis.

In a discussion of the medical and surgical aspects of Charcot joints Epstein [203] brings out that the condition is primarily an orthopedic problem. Antisyphilitic treatment is valueless so far as the arthropathy is concerned.

THE TREATMENT OF NEUROSYPHILIS

The Choice of Method.—Wagner-Jauregg [204] reviews the general considerations involved in the treatment of patients with neurosyphilis. In his opinion the most important of these is to realize that neurosyphilis develops early in the course of syphilitic infection and should be detected by early routine examination of the cerebrospinal fluid. A positive reaction at this stage does not necessitate the immediate induction of fever; the simple methods should be tried first. On the other hand, fever therapy is urgently indicated if the patient comes under observation with clinical neurosyphilis.

The discussion regarding the superiority of inoculation malaria over fever induced by artificial means or vice versa seems for the moment to have abated. In a preliminary report of a proposed long-term study,

---

199. Langworthy, O. R.; Dees, J. E., and Lewis, L. G.: Abnormalities of Micturition Due to Syphilis of the Nervous System, Am. J. Syph., Gonor. & Ven. Dis. **20**:364 (July) 1936.

200. Rubritius, H.: Die Miktionsstörungen der Tabiker, Wien. klin. Wchnschr. **50**:311 (March 5) 1937.

201. Muschet, M.: Cystometric Studies: The Value of Follow-Up Examinations, Am. J. M. Sc. **192**:693 (Nov.) 1936.

202. Bujadoux, A., and Gourevitch, F.: Les troubles du pré-Argyll-Robertson, Presse méd. **45**:550 (April 10) 1937.

203. Epstein, S. H.: Medical and Surgical Aspects of Charcot Joints, Am. J. Syph., Gonor. & Ven. Dis. **20**:386 (July) 1936.

204. Wagner-Jauregg, J.: Die Behandlung der luetischen Erkrankungen des Nervensystems, Therap. d. Gegenw. **77**:385 (Sept.) 1936.

however, Barnacle and his co-workers [205] observed no significant difference in the clinical outcome for patients treated by one means or the other. Both groups had received tryparsamide.

For patients in whom treatment with fever is indicated the question which has been most recently raised concerns the desirability or the best method of adding tryparsamide to the scheme of treatment.

The Combination of Fever Therapy with Tryparsamide.—Maletz and Solomon [206] present the results of their study of 87 patients with dementia paralytica who had been treated with malaria followed by tryparsamide. They were able to show better results for this group than for patients treated with malaria alone. Like Wile and Hand,[207] they discovered no correlation between the clinical course and the serologic findings in the cerebrospinal fluid.

Hinsie and Blalock [208] observed a group of 146 patients for from six months to four years after the administration of ten paroxysms of artificially induced fever, which totaled about seventy hours. These patients fell into three groups: (1) those who had fever only, (2) those who received tryparsamide after the course of fever treatment and (3) a smaller number who received tryparsamide just before each fever treatment. These authors conclude that while benefit is derived from treatment with fever alone, the best results follow the use of tryparsamide subsequent to fever therapy. They especially bring out, however, that there seems to be no advantage to the administration of a dose of tryparsamide just before each fever treatment.

The Results of Fever Treatment of Neurosyphilis.—Wile and Hand [207] are much encouraged by the average course of events in their group of 474 patients treated with malaria. One hundred and eighty-two of these patients came under observation with dementia paralytica; the remainder had various other forms of neurosyphilis. In patients with juvenile dementia paralytica little benefit was observed, but more than half the adults showed improvement. This was especially true for those who had had a relatively acute onset of symptoms and who did not have obvious deterioration. Half the patients with tabes and 95 per cent of those with asymptomatic neurosyphilis achieved a satisfactory

205. Barnacle, C. H.; Ebaugh, F. G., and Ewalt, J. R.: Treatment of Dementia Paralytica: Comparative Study of Combined Artificial Hyperpyrexia and Tryparsamide Versus Therapeutic Malaria; a Preliminary Report, J. A. M. A. **107**:1031 (Sept. 26) 1936.

206. Maletz, L., and Solomon, H. C.: Spinal Fluid Reaction in General Paresis as Modified by a Combination of Therapeutic Malaria and Tryparsamide, Am. J. Syph., Gonor. & Ven. Dis. **21**:287 (May) 1937.

207. Wile, U. J., and Hand, E. A.: Ten Years' Experience with Malaria in Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **20**:630 (Nov.) 1936.

208. Hinsie, L. E., and Blalock, J. R.: Treatment of General Paralysis by Ultra High-Frequency Heating, New York State J. Med. **36**:1951 (Dec. 15) 1936.

result. The authors particularly emphasize in this group the lack of correlation between the clinical course and the changes in the reactions to serologic tests of the cerebrospinal fluid.

Paulian [209] succeeded in producing malaria in 1,165 (86 per cent) of a group of 1,359 patients with dementia paralytica. The remainder were immune to inoculation. Seventy-four per cent of those in whom malaria ran a typical course showed either "cure" or marked improvement for varying periods of observation.

Nichole and his co-workers [210] and Wheelock [211] report smaller series of patients, with essentially similar results. In a review of the literature Neymann [212] found reports on 853 patients with parenchymatous neurosyphilis to whom treatment with electropyrexia had been given. Of the 754 patients with dementia paralytica, 213 (28 per cent) were accredited with complete remission, and 260 (35 per cent) were reported as being improved. Twenty, or 2.5 per cent, had died as a result of treatment. Only 9 patients with juvenile dementia paralytica treated with electropyrexia have been reported on. Of these, 2 were markedly improved, 5 were improved and 2 were unimproved. Ninety patients with tabes are reported on, 54 being improved and 36 unimproved.

Bennett [213] points out that neither chemotherapy nor inoculation malaria relieves the lightning pains or gastric crises of tabes dorsalis of more than half the patients so treated. In contrast, by a combination of simultaneous chemotherapy and artificially induced fever he was able to relieve symptoms in all of his 11 patients.

The Determination of the Prognosis of Inoculation Malaria.—Paulian [214] advances the interesting suggestion that the determination of the permeability of the blood-brain and the blood-cerebrospinal fluid barriers to arsenic before and after malaria therapy may be a valuable

209. Paulian, D.: La malariothérapie dans le traitement des syphilis nerveuses, Ann. d. mal. vén. **31**:561 (Aug.) 1936.

210. Nichole, J. E.; Harrison, G. J.; Nichol, W. D., and Hutton, E. L.: A Follow-Up Study of General Paralysis, with Special Reference to Malarial Therapy, Proc. Roy. Soc. Med. **30**:623 (March) 1937.

211. Wheelock, M. C.: The Treatment of Paresis Based on an Analysis of One Hundred and Thirteen Patients, J. Iowa M. Soc. **27**:107 (March) 1937.

212. Neymann, C. A.: The Effect of Artificial Fever on the Clinical Manifestations of Syphilis and the Treponema Pallidum, Am. J. Psychiat. **93**:517 (Nov.) 1936.

213. Bennett, A. E.: Fever Therapy in Tabes Dorsalis: Relief of Gastric Crises and Lightning Pains by the Use of the Kettering Hypertherm, J. A. M. A. **107**:845 (Sept. 12) 1936.

214. Paulian, D.: La perméabilité des méninges à l'arsenic dans la paralysie générale avant et après la malariothérapie, Ann. de méd. **39**:375 (April) 1936; Ueber den feinen Wirkungsmechanismus der Malariatherapie in den Veränderungen hämato-meningealer Schranken, Wien. med. Wchnschr. **87**:264 (March 6) 1937.

prognostic sign. Normally, he says, arsenic may be detected in the cerebrospinal fluid only in traces, if at all, after the intravenous injection of a trivalent arsenical. For 12 patients with dementia paralytica, however, the arsenic content of the cerebrospinal fluid was repeatedly determined by the method of Martin and Pien (which he fully describes) from four to ten hours after the intravenous injection of 0.45 Gm. of neoarsphenamine. Before the induction of malaria the average arsenic content of the cerebrospinal fluid was 0.001 Gm. per hundred cubic centimeters; afterward the value had fallen to 0.0002 Gm. per hundred cubic centimeters. In general, also, the lowest values after inoculation malaria were obtained for the patients who showed the greatest clinical improvement. Paulian feels therefore that, in addition to the great theoretical interest, the determination may be of some practical importance.

Artificially Induced Fever; General Considerations.—Krusen [215] presents a summary of current knowledge concerning fever therapy produced by physical means. The discussion of the physiology of artificially induced fever is especially complete. Stecher and Solomon [216] add a detailed study of the complications of artificially induced fever based on 1,000 consecutive treatments. Nausea with vomiting was the most common complication which they observed; circulatory collapse, the most serious.

Wilbur and Stevens [217] report the morbid anatomic observations for 2 patients who died after treatment in an electric lamp cabinet and, in comparison, those for a third patient who died of sunstroke. They conclude:

> The most consistent findings in these three cases were congestion, petechial hemorrhages and diffuse early hepatic necrosis. Evidence of damage to the central nervous system was found in only one case. This was characterized by degenerative changes in the astrocytes.

Blood Versus Mosquito for Transmission of Malaria.—Boyd and his collaborators [218] have been engaged in the development of a method for easily maintaining facilities for the transmission of therapeutic malaria by mosquitoes. The observations of Kusch and others [219] show

215. Krusen, F. R.: The Present Status of Fever Therapy Produced by Physical Means, J. A. M. A. **107**:1215 (Oct. 10) 1936.

216. Stecher, R. M., and Solomon, W. M.: The Complications and Hazards of Fever Therapy: Analysis of One Thousand Consecutive Fever Treatments with the Kettering Hypertherm, Ann. Int. Med. **10**:1014 (Jan.) 1937.

217. Wilbur, E. L., and Stevens, J. B.: Morbid Anatomic Changes Following Artificial Fever, with Report of Autopsies, South. M. J. **30**:286 (March) 1937.

218. Boyd, M. F.; Stratmen-Thomas, W. K., and Kitchen, S. F.: Modifications in a Technique for the Employment of Naturally Induced Malaria in the Therapy of Paresis, Am. J. Trop. Med. **16**:323 (May) 1936.

219. Kusch, E.; Milam, D. F., and Stratmen-Thomas, W. K.: General Paresis Treated by Mosquito-Inoculated Vivax (Tertian) Malaria, Am. J. Psychiat. **93**: 619 (Nov.) 1936.

that the efforts are worth while. In their comparative study of 72 patients treated by mosquito inoculation and 363 patients treated by blood inoculation, these authors discovered that the main differences in the clinical course was that in the former patients it was milder, thereby permitting a longer period of infection. The differences in results were striking. Twenty-six per cent of the patients given mosquito inoculation gained a sustained remission, and 49 per cent were improved; for those given blood inoculation the results were 19 and 36 per cent, respectively.

Boyd and Kitchen [220] show that Plasmodium falciparum may be kept in mosquito culture and is readily transmissible to man. In contrast to the situation with Plasmodium vivax, the Negro possesses no racial immunity to P. falciparum. A small clinical experience indicates that the organism has great powers of invasiveness and, therefore, that it must be used with caution. Clinical results, however, are promising.

Blackwater Fever.—Foy and Kondi [221] inoculated 106 patients who had various psychoses with blood from some one of a group of 58 patients with blackwater fever. In none of the patients who were inoculated did hemoglobinuria develop.

Fever Therapy as an Office Procedure.—Davison, Lowance and Barnett [222] advocate the employment of fever therapy as an office procedure. McClure,[223] on the other hand, adopts a much more defensible position:

> Fever therapy is not simple . . . and to be safely given demands special training. . . . At the present time there are appearing . . . advertisements of fever-producing machines for office use. Nothing is so apt to discredit fever therapy as this indiscriminate use under the belief that it is an innocuous thing.

Special Methods of Fever Therapy.—Kulchar and Anderson [224] recommend the use of divided doses of typhoid H antigen for the pro-

220. Boyd, M. F., and Kitchen, S. F.: A Further Note on the Infectiousness of Anopheline Mosquitoes Infected with P. Vivax and P. Falciparus, Am. J. Trop. Med. **17**:245 (March) 1937; Observations on Induced Falciparum Malaria, ibid. **17**:213 (March) 1937.

221. Foy, H., and Kondi, A.: Researches on Blackwater Fever in Greece: IV. Experimental Investigations into the Existence of Haemolytic Strains of Malaria and/or Other Specific Parasites in Blackwater Fever, Ann. Trop. Med. **30**:423 (Dec.) 1936.

222. Davison, H. M.; Lowance, M. I., and Barnett, C. F.: Hyperpyrexia: An Evaluation of Its Use in Office Practice, M. Rec. **143**:253 (March 18) 1936.

223. McClure, R. D.: Artificial Fever Therapy, South. M. J. **29**:704 (July) 1936.

224. Kulchar, C. V., and Anderson, L. E.: Divided Doses of Typhoid H Antigen Vaccine in the Treatment of Neurosyphilis, Am. J. Syph., Gonor. & Ven. Dis. **21**:413 (July) 1937.

duction of fever in the treatment of neurosyphilis, especially of the aged or the infirm. Ogata [225] suggests inoculation with the virus of typhus as a ready means of producing fever! Werner [226] employed a less severe rickettsia infection (five day fever) for the same purpose.

Acetarsone.—Pakenham-Walsh and Rennie [227] report encouraging results from the preliminary study of the oral administration of acetarsone to patients with dementia paralytica. They feel that the drug should have an extensive trial.

The Treatment of Atrophy of the Optic Nerve.—Since 1916 Schacherl [228] has treated 114 patients with primary atrophy of the optic nerve by the subdural method. Sixty-nine of the patients were observed for more than three years. In 53 of this group (77 per cent) the author believes that treatment was successful.

An interesting theoretical discussion of the genesis of atrophy of the optic nerve is presented by Lauber.[229] This author seeks to explain the underlying phenomena as due to an interaction between a fall in systemic blood pressure and a rise in intra-ocular tension, thereby causing mechanical impeding of the circulation to the retina and optic nerve.

Folk,[230] working on a similar theory, combines paracentesis bulbi with the subcutaneous injection of atropine in the treatment of various conditions of the retina and optic nerve. Some benefit was obtained by 6 patients with primary atrophy of the optic nerve whom he treated by this method.

SYPHILIS AND PREGNANCY

The fact that untreated syphilis in the mother is capable of exerting a deleterious effect on the outcome of pregnancy is now well established and needs no further documentation. The frequency of this effect and the conditions other than treatment of the disease in the mother which

225. Ogata, N.: Ueber Rickettsiatherapie der Neurosyphilis, Wien. klin. Wchnschr. **49**:1225 (Oct. 2) 1936.

226. Werner, H.: Neuere Ergebnisse aus dem Gebiete der Tropenhygiene: V. Zur Methodik der Arzneimittelprüfung bei Malaria und zur Fieberbehandlung der Paralyse (Rickettsienimpfung), Deutsche med. Wchnschr. **62**:903 (May 29) 1936.

227. Pakenham-Walsh, R., and Rennie, A. T.: Oral Administration of Stovarsol in Cases of Neurosyphilis Certified as Insane, Lancet **1**:982 (April 24) 1937.

228. Schacherl, M.: Zwanzig Jahre endolumbaler Salvarsanbehandlung der Atrophia nervi optici tabetica, Wien. klin. Wchnschr. **50**:313 (March 5) 1937.

229. Lauber, H.: Treatment of Atrophy of the Optic Nerve, Arch. Ophth. **16**:555 (Oct.) 1936.

230. Folk, M. L.: Paracentesis and Atropine in the Treatment of Optic and Retinal Atrophies: Preliminary Report, Am. J. Ophth. **20**:511 (May) 1937.

modify it are, however, still in need of clarification. Paley's [231] communication is therefore timely. In a study of 617 pregnancies of women with syphilis this author discovered that 173 (28 per cent) eventuated unfavorably as a direct result of the maternal infection.

The effect of the duration of syphilis in the mother on the outcome of pregnancy is strikingly shown. Disregarding other factors, the outcome of the pregnancy was unfavorable in 51 per cent of the instances in which the mother had had syphilis for less than two years, in only 25 per cent of the instances in which the infection was of more than two but less than five years' duration and in only 19 per cent of the instances in which the infection had been present five years or more.

The author demonstrates equally clearly that in this group the end-result of the pregnancy is related to the amount of antisyphilitic treatment which the mother receives during pregnancy. Unfavorable end-results due to syphilis occurred in 46 per cent of the cases in which the mother received less than 4 injections of an arsenical plus heavy metal, but in only 27 per cent of the cases in which from 4 to 7 injections were given and in only 14 per cent of the cases in which 8 or more injections were given. The influence of the trimester in which treatment was begun was less striking and seemed to be related only to the total amount of treatment administered.

The Influence of Pregnancy on Syphilis.—There has long been the clinical impression that pregnancy exerts a beneficial effect on the course of syphilitic infection. Kemp [232] sought to examine the question experimentally. Four groups each of 12 rabbits were employed; all were infected with syphilis by a standard method. A group of females was repeatedly bred after infection until each animal had had three litters. A group of females and a group of males were treated with filtered urine of pregnant women for fifteen weeks, and the fourth group, half of them males and half of them females, were carried as controls. The results suggested to Kemp that while pregnancy exerts an appreciable inhibiting effect on the course of syphilitic infection, it is not the only factor responsible for the altered course of the disease in the female.

CONGENITAL SYPHILIS

The Genesis of Congenital Syphilis.—Levaditi and his group [233] theorize concerning the mode of infection of the child with congenital

231. Paley, S. S.: Syphilis in Pregnancy, New York State J. Med. **37**:585 (March 15) 1937.

232. Kemp, J. E.: The Effect of Pregnancy and of Female Sex Hormones in Modifying the Course of Syphilis in Experimental Animals, J. Infect. Dis. **60**:32 (Jan.-Feb.) 1937.

233. Levaditi, C.; Goldman, M., and Rousset-Chabaud: Mécanisme de la transmission héréditaire de l'infection syphilitique, Compt. rend. Soc. de biol. **120**:854, 1935.

syphilis, particularly with regard to the manner by which the nonsyphilitic children of a syphilitic mother escape infection. After considering the various possibilities they conclude that the spirochete must be filtered out of the maternal circulation by the placenta. Local factors in that organ then determine whether or not fetal infection occurs. Kemp and Rosahn [234] reached somewhat similar conclusions from their unsuccessful attempts to produce congenital syphilis in the rabbit. They concluded that either the placenta filters out the spirochete or the fetus destroys it; the evidence favors the former hypothesis.

General Considerations.—Hoffmann,[235] Maddox [236] and many others present general summaries of the problems of congenital syphilis which do not lend themselves well to review. Cregor and Dalton [237] plead for the development of methods for the earlier accurate diagnosis of syphilis in the new-born.

Clinical Phenomena in Congenital Syphilis.—Josephs [238] observes that anemia is present in a large percentage of children with congenital syphilis. Further, he says that congenital syphilis is one of the commonest causes of severe anemia during the first three months after the neonatal period.

Glickman and Minsky [239] call attention to the occurrence of enlargement of one sternoclavicular articulation in patients with late congenital syphilis. Jung [240] discusses the various skeletal manifestations of congenital syphilis which he observed in roentgenograms of 6 stillborn syphilitic fetuses and 56 syphilitic infants under 1 year of age.

"Bismuth Lines" in the Bones of Infants.—Caffey [241] studied roentgenograms of the bones of children under treatment with bismuth and of those whose mothers had received bismuth during pregnancy. He

234. Kemp, J. E., and Rosahn, P. D.: Experimental Study of Congenital Syphilis, Including a Study of the Infectiousness of Blood, Uterus and Placenta of Pregnant Rabbits with Early Syphilis, Bull. Johns Hopkins Hosp. **60**:45 (Jan.) 1937.

235. Hoffmann, E.: Congenital Syphilis in the Light of Thirty Years' Investigation of the Spirochete and Twenty-Five Years' Experience with Salvarsan, J. Pediat. **9**:569 (Nov.) 1936.

236. Maddox, R. C.: Congenital Syphilis, Arch. Pediat. **53**:692 (Oct.) 1936.

237. Cregor, F. W., and Dalton, J. E.: Syphilotoxemia in the New-Born, Arch. Dermat. & Syph. **35**:580 (April) 1937.

238. Josephs, H. W.: Anaemia of Infancy and Early Childhood, Medicine **15**: 307 (Sept.) 1936.

239. Glickman, L. G., and Minsky, A. A.: Enlargement of One Sterno-Clavicular Articulation: A Sign of Congenital Syphilis, Radiology **28**:85 (Jan.) 1937.

240. Jung, T. S.: Congenital Bone Syphilis: Roentgenologic Diagnosis in Infants Under One Year of Age, Chinese M. J. **50**:352 (April) 1936.

241. Caffey, J.: Changes in the Growing Skeleton After the Administration of Bismuth, Am. J. Dis. Child. **53**:56 (Jan.) 1937.

found a definite relation both between the time (in the stage of the development of the fetus or child) that the bismuth was administered and the position of the "bismuth line" in the long bones and between the amount of bismuth which had been given and the width of the "metallic" shadow in the roentgenogram. Experimental studies of growing puppies, however, seemed to indicate that the roentgen-opaque shadow laid down at the epiphysial line after the administration of bismuth was largely a calcified cartilaginous matrix, with a relatively low content of bismuth.

The Eye in Congenital Syphilis.—A first examination of the statistics which Berens, Kerby and McKay [242] present seems to suggest that syphilis is the cause of only 5.3 per cent of blindness in children. These authors bring out, however, that "hereditary and congenital" blindness, which accounts for more than half the blindness among children in the schools for the blind, must include some blindness due to syphilis, so that the actual incidence of syphilitic blindness is higher than appears.

From a group of 247 children with congenital syphilis Lennarson and Jeans [243] selected 143 for special study of the condition of the eyes. Sixty-six per cent of this specially studied group (38 per cent of the entire group) were found to have some syphilitic lesion of the eye. Forty-three per cent of all the children over 2 years of age manifested interstitial keratitis. The maximum frequency of this condition occurred at the age of 8 (57 per cent). Chorioretinitis was found in only 1 infant but in 13 per cent of the older children whose fundi were examined. Atrophy of the optic nerve was about half as frequent.

For one third of the 1,010 patients with late congenital syphilis studied by the Cooperative Clinical Group, Cole,[244] acting as spokesman, says that interstitial keratitis was the principal initial diagnosis.

Juvenile Dementia Paralytica.—A careful study of the pathologic changes in the brains of 7 children with juvenile dementia paralytica is reported by Haas.[245] He observed that the changes, in general, were those characteristic of dementia paralytica in adults, but with certain additions. The changes in the children's brains were more striking, there was greater evidence of degeneration and lesions were present in the cerebellum in all 7 cases.

242. Berens, C.; Kerby, C. E., and McKay, E. C.: The Causes of Blindness in Children: Their Relation to Preventive Ophthalmology, J. A. M. A. **105**:1949 (Dec. 14) 1935.

243. Lennarson, V. E., and Jeans, P. C.: Congenital Syphilis of the Eyes: A Clinical Study, Am. J. Syph., Gonor. & Ven. Dis. **21**:90 (Jan.) 1937.

244. Cole, H. N., and others: Late Prenatal Syphilis, Arch. Dermat. & Syph. **35**:564 (April) 1937.

245. Haas, H. T. A.: Beitrag zur Pathologie und Pathogenese der juvenilen Paralyse, Ztschr. f. d. ges. Neurol. u. Psychiat. **156**:405 (Oct. 16) 1936.

The picture of juvenile dementia paralytica which Grotjahn [246] presents is not a happy one, but it is in keeping with the experience of others. This author treated with malaria 57 children who had dementia paralytica. The average age at the onset of symptoms was 14 years for the 25 who had had no previous treatment, 13 years for the 22 who had had treatment in childhood and 9.3 years for the 10 who had been treated in infancy. In none of these children, however, had treatment been adequate. None gained a complete remission after malaria treatment, 4 could not be traced and, of the remainder, 18 had a partial remission and 35 were unimproved or dead.

The Treatment of Congenital Syphilis.—For the treatment of congenital syphilis Givan and Villa [247] recommend the use of acetarsone intravenously. They have given 43 children a total of 1,010 injections of this drug in weekly doses of from 0.2 to 1 Gm., and they say that it is useful, safe and well tolerated.

Gerth [248] sounds a note of caution regarding the use of acetarsone. He observed death attributable to the drug in a child 3½ months of age, and he knows of other instances. He feels therefore that if the drug is to be used, it should be given in small doses.

THIRD GENERATION SYPHILIS

Wendel [249] presents a case of third generation syphilis which fulfils all the Fournier-Finger criteria. The case of Rein and Shostac [250] is also convincing and fails to fulfil the formal criteria only because in the second generation lesions of syphilis did not develop shortly after birth.

BEJEL

Bejel has been brought to light entirely through the contributions of Hudson,[251] who observed it during his service as chief of the clinic in

246. Grotjahn, M.: Zur Klinik und Psychologie der juvenilen Paralyse, Monatschr. f. Psychiat. u. Neurol. **92**:299 (Feb.) 1936; **93**:19 (March) 1936.

247. Givan, T. B., and Villa, G.: The Intravenous Use of Acetarsone in Congenital Syphilis, J. Chemotherapy **13**:97 (Oct.) 1936.

248. Gerth, R.: Zur Frage der Heilung der kongenitalen Lues des Säuglings mit kleinen Spirociddosen, Monatschr. f. Kinderh. **67**:46 (Sept. 19) 1936.

249. Wendel, F.: Ein Beitrag zur Frage der Uebertragung der kongenitalen Syphilis auf die nächste Generation, Med. Klin. **32**:976 (July 17) 1936.

250. Rein, C. R., and Shostac, F.: Probable Case of Third Generation Syphilis: Report of a Case, Arch. Dermat. & Syph. **34**:877 (Nov.) 1936.

251. Hudson, E. H.: Hyperkeratoses and Depigmentations in Bejel, Ann. Trop. Med. **30**:3 (April) 1936; Bejel: Nonvenereal Syphilis, Arch. Dermat. & Syph. **33**:994 (June) 1936. Hudson, E. H., and Crosley, S. S.: The Influence of Bejel on the Second Generation, Brit. J. Dermat. **48**:288 (June) 1936. Hudson, E. H.: Mucocutaneous Syphilis (Bejel) in Syria, New England J. Med. **215**:392 (Aug. 27) 1936; Bejel—The Childhood Syphilis of the Bedouins: Oral Manifestations, J. Am. Dent. A. **24**:219 (Feb.) 1937; Kahn and Kolmer-Wassermann Reactions in Bejel, Am. J. Syph., Gonor. & Ven. Dis. **21**:45 (Jan.) 1937.

Deir-ez-Zor, Syria. Bejel, he says, is an Arabian name for the nonvenereal syphilis usually acquired during childhood by the seminomad Bedouin villagers of the middle division of the Euphrates valley. It is extremely prevalent (he estimates that 90 per cent of the adults either have or have had the disease) and participates in many of the clinical characteristics of yaws. It occurs, however, far north of the usual geographic locations in which yaws is seen, and there are certain differences in the clinical manifestations of the two diseases.

YAWS

Not much of the considerable literature on yaws is proper material for this review. A few contributions, however, which bear on the relation between yaws and syphilis are of interest. Turner [252] presents the results of an extensive series of inoculation experiments on 79 patients with yaws and 10 with syphilis and concludes:

> In man, yaws confers an immunity to reinfection. Resistance to auto-inoculation becomes manifest early in the course of the disease and obtains in most persons during the period in which active lesions are present. Immunity to reinoculation of heterologous strains of yaws spirochetes develops slowly during the course of the natural disease. Within the first years, reinoculation may give rise to a modified or an abortive attack of yaws but after a period of 10 years, the majority of yaws-infected persons are refractory to reinoculation. Interruption of the normal course of the disease by treatment seems to retard the development of immunity.
>
> Syphilis also confers an immunity to yaws which is as great as, if not greater than, that conferred by yaws itself.

In the experimental rabbit the same author [253] discovered that organisms from patients with yaws and from patients with syphilis produced characteristic and different disease processes and that each retained its identity during many passages through animals.

Weller [254] has been conducting a painstaking histopathologic study of the viscera of patients with "Haitian treponematosis" which were submitted to him from the Haitian General Hospital at Port au Prince. At the conclusion of the more recent article [254b] he says:

> In view of the impossibility of establishing an indubitable clinical diagnosis for each patient, this study must not be considered as offering certain proof of either the unity or the duality of yaws and syphilis. It is intended only as an objective presentation of factual material. However, one of three conditions must exist: either yaws and syphilis are essentially the same disease; or the group of patients

252. Turner, T. B.: The Resistance of Yaws and Syphilis Patients to Reinoculation with Yaws Spirochetes, Am. J. Hyg. **23**:431 (May) 1936.

253. Turner, T. B.: Studies on the Relationship Between Yaws and Syphilis, Am. J. Hyg. **25**:477 (May) 1937.

254. Weller, C. V.: (*a*) The Pathology of the Aorta in Haitian Treponematosis, Am. J. Syph., Gonor. & Ven. Dis. **20**:467 (Sept.) 1936; (*b*) The Visceral Pathology in Haitian Treponematosis, ibid. **21**:357 (July) 1937.

here considered has an extremely high incidence of syphilis and the evidences of this disease alone are apparent in the viscera; or yaws and syphilis, if different diseases, produce identical visceral lesions.

RESISTANT SYPHILIS

Drug Resistance.—Netherton [255] reports 2 instances of conjugal syphilis of the early type in each of which only the wife showed resistance to drugs. In 1 case the infection was resistant to the arsenicals and to bismuth and mercury, while in the other case resistance was manifested to three of the most commonly used arsenicals. This resistance to both arsenic and the heavy metals, says the author, tends to invalidate the theory of a strain of S. pallida which is resistant to arsphenamine.

The patient whom Hood [256] reports on maintained lesions in the mouth which showed S. pallida on dark field illumination for almost two years. During the first year intensive treatment with arsphenamine and mercury was given, after which there was a lapse in treatment. When the patient returned the lesions healed promptly when treated with an experimental arsenic preparation, and no recurrences were observed. Treatment was continued with arsphenamine, and sixteen years later the patient was found to be clinically well. There was, however, still a positive reaction to serologic tests for syphilis.

Schoch [257] reports an unusual experience. He inoculated rabbits with spirochetes from a patient with treatment-resistant syphilis and was able to retain the resistance of the strain during passages through animals.

Seroresistance.—O'Leary [258] points out that the manifestation of a persistently positive reaction to serologic tests for syphilis during treatment has many possible interpretations. The correct one may be obtained by the interpretation of the history, physical examination and serologic tests of blood and cerebrospinal fluid by a shrewd clinician.

INTERRELATION OF SYPHILIS AND TUBERCULOSIS AND OTHER FEATURES

Pulmonary Tuberculosis.—Leader [259] brings up the problems which the diagnosis and treatment of pulmonary tuberculosis may present

255. Netherton, E. W.: Arsphenamine-Resistant Syphilis, Arch. Dermat. & Syph. **35**:607 (April) 1937.

256. Hood, B. J.: An Unusual Case of Arsphenamine Resistance, Am. J. Syph., Gonor. & Ven. Dis. **21**:97 (Jan.) 1937.

257. Schoch, M. A.: Fortdauer der Therapieresistenz eines Pallidstammes im Tierversuch, Klin. Wchnschr. **16**:306 (Feb. 27) 1937.

258. O'Leary, P. A.: Wassermann Fastness, Journal-Lancet **56**:464 (Sept.) 1936.

259. Leader, S. A.: Pulmonary Tuberculosis and General Paresis, Am. Rev. Tuberc. **34**:776 (Dec.) 1936.

when it occurs in patients hospitalized because of mental disease. In patients with dementia paralytica, because of their generally poor condition, tuberculosis is particularly likely to develop and this of course precludes fever therapy. The patient must be treated for the tuberculosis, if for no other reason than to prevent the spread of the disease to others, and the author recommends that tryparsamide be used for the treatment of the neurosyphilis.

Old Age.—In discussing the treatment of elderly persons with syphilis Netherton [260] brings out the necessity of individualization. For patients with active syphilis in any stage treatment must be given with sufficient vigor to control progression, heal lesions and prevent infectiousness. For elderly persons with late quiescent syphilis, however, treatment may be gentle or may be omitted.

Race.—Hazen [261] estimates that syphilis is at least twice as prevalent among Negroes as in the white race and points out the terrific cost which it levies. There are certain racial differences in the clinical course of the disease, but the response to treatment is the same.

Vonderlehr and his collaborators [262] compared the morbidity rates for three groups of Negro men: 399 with syphilis who had never received treatment, 201 who were presumably normal and 275 with syphilis who had received treatment during the first two years of the infection. They say:

> The results indicate that the cardiovascular system is the most commonly involved in the late syphilitic process and the aorta is the most commonly involved structure in so-called latent syphilis in the adult male Negro.
>
> Morbidity in the male Negro with untreated syphilis far exceeds that in a comparable presumably nonsyphilitic group.
>
> Adequate antisyphilitic treatment prevented all forms of clinical relapse during the first fifteen years of the infection, whereas only one fourth of the Negroes with untreated syphilis were normal.
>
> Cardiovascular and central nervous system involvement were from two to three times as common in the untreated syphilis group as in a comparable group receiving even inadequate treatment.

GENERAL CONSIDERATIONS

Almkvist [263] is dissatisfied with the time-honored division of syphilis into three stages and proposes a new classification, which he bases on

260. Netherton, E. W.: The Management of Syphilis in Elderly Persons, Cleveland Clin. Quart. **3**:205 (July) 1936.

261. Hazen, H. H.: Syphilis in the American Negro, Am. J. Syph., Gonor. & Ven. Dis. **20**:530 (Sept.) 1936.

262. Vonderlehr, R. A.; Clark, T.; Wenger, O. C., and Heller, J. R., Jr.: Untreated Syphilis in the Male Negro: A Comparative Study of Treated and Untreated Cases, J. A. M. A. **107**:856 (Sept. 12) 1936.

263. Almkvist, J.: Die Ergebnisse meiner histologischen Untersuchungen über syphilitische Veränderungen, Wien. med. Wchnschr. **86**:1266 (Nov. 14) 1936; The Pathology of Syphilis in a New Light, Brit. J. Dermat. **49**:1 (Jan.) 1937.

the histopathologic pictures of the different lesions. The classification is rather complicated and does not seem destined to gain general use.

Stokes,[42b] in the Prosser White oration, sums up the practical problems in the control of syphilis and the methods which are at hand for solving them.

Chesney [264] discusses the needs for research on the control of syphilis before the Conference on Venereal Disease Control. After a step by step summary of the needs in all the various phases of the problem, he concludes:

> The real answer to the whole question is, of course, quite simple. There are only two needs, as is always the case in matters of research. The first of these is to find men and women with imagination and ideas, and then interest them in the problem; the second is to secure for these individuals the means which will permit them to work out their ideas unhampered. If these two needs can be fulfilled, then all that is necessary is to let nature take its course. One does not need to worry about the result.

264. Chesney, A. M.: Research Needs in the Control of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. **21**:121 (March) 1937.

CORRECTION

In a recent article entitled "Influence of Copper and a Liver Fraction on Retention of Iron" (ARCH. INT. MED. **60**:474 [Sept.] 1937), Barer and Fowler erroneously used the term liver rather than liver extract in referring to the results obtained by Cheney and Niemand (footnote 11) and by Powers and Murphy (footnote 12). In 1931 Powers and Murphy stated, "Liver extract is of no value in the treatment of these types of chronic secondary anemia" (The Treatment of Secondary Anemia, *J. A. M. A.* **96**:504 [Feb. 14] 1931). Murphy, however, in a subsequent article stated that in secondary anemia "treatment by means of intramuscular injections of solution of liver extract (Lederle) together with adequate doses of iron by mouth is the most effective" (Treatment of Secondary Anemia, with Special Reference to the Use of Liver Extract Intramuscularly, ARCH. INT. MED. **51**:656 [May] 1933).

Book Reviews

Eugenical Sterilization: A Reorientation of the Problem. By Abraham Myerson, J. G. Ayer, T. J. Putnam, C. E. Keeler and Leo Alexander, the Committee of the American Neurological Association for the Investigation of Eugenical Sterilization. Price, $3. Pp. 211. New York: The Macmillan Company, 1936.

This book constitutes the report of the special committee which was appointed in 1934 by the American Neurological Association to survey the problem of eugenical sterilization. It is a clear, straightforward and readable discussion of the problem of heredity in relation to neurology and psychiatry and of the feasibility of attempting to control diseases with a hereditary tendency by a program of sterilization, either compulsory or voluntary. The writer of each section has reviewed both the older and the more recent literature thoroughly and discusses his problem in the light of the best modern medical and genetic thought.

The medical literature dealing with heredity and sterilization has hitherto presented an almost insurmountable obstacle to any one interested in this subject. Thoughtful perusal indicates that it can truthfully be said that this book is a valuable contribution to medical and genetic literature, not only because of its authoritative and penetrating analysis of the problems considered but because of the many erroneous theories and hypotheses, until recently firmly embedded in medical thought, which it so conclusively proves to be valueless, without foundation and even absurd.

It is impossible to give in a short space all the subjects that are considered in detail. Some of the more important conclusions, however, are too valuable to omit. An adequate history of eugenics and sterilization is given, and a chapter is devoted to the pertinent laws now in force in the various states of the United States and in foreign countries.

In considering the main arguments for sterilization some interesting points are brought out in the present work. It is demonstrated that mental disease is actually not increasing and that it is only the recognition and commitment of psychiatric patients to institutions that is increasing in locations where better facilities for diagnosis and treatment of these conditions have developed. The authors conclude that "there is nothing to indicate that mental disease and mental defectives are increasing, and from this standpoint there is no evidence of a biological deterioration of the race. What is certain is that the hospital population is increasing." The authors believe that too much stress has been laid on the expense of caring for the mentally sick.

The chapter dealing with points of view regarding sterilization contains the opinions of many persons regarding sterilization, both pro and con. It is impossible to give these opinions in their entirety, but it is evidently the author's intention that the reader should recognize that the statements issued by exponents of a sweeping program of compulsory sterilization are misleading and, to say the least, "overdogmatic and socially excessive." The majority of recent opinions quoted are in favor of a properly regulated program of voluntary sterilization limited to persons afflicted with disorders which have been definitely shown to be transmissible.

There is an excellent and well condensed chapter on genetics and its relation to eugenics. The most prominent geneticists of the present time have expressed the opinion that the race can be benefited by good breeding and by the elimination of undesirable stocks, but they are not convinced that man knows enough about mental diseases and the effects of the social structure to manipulate in a successful way the procreation of the race.

There is an excellent chapter on the inheritance of mental diseases which represents a cautious attempt to review the situation as it exists today. The

authors reach the important conclusion that there is little real information on which to base any farflung theory of the heredity of psychoses or feeblemindedness. They believe that no definite evidence exists which warrants the postulate of any widespread unitary trait back of the psychoses, feeblemindedness, epilepsy and the like.

The most recent studies on the inheritance of manic depressive psychosis, dementia praecox, feeblemindedness and epilepsy are considered in detail but cannot be quoted here. When modern methods are employed, the only definite statement that can be made in regard to the inheritance of dementia praecox, manic depressive psychosis, epilepsy and feeblemindedness is that these conditions occur in certain families in a higher incidence than in the general population but that inheritance in a mendelian ratio cannot be demonstrated.

There is a short chapter on chronic progressive neurologic diseases known to have some tendency toward hereditary transmission. This chapter does not deal with all the neurologic conditions known to have a hereditary tendency but rather gives a brief summary of some of the literature concerning the diseases in which hereditary transmission is most marked. A chapter is also devoted to a discussion of the possible effect of a sterilization program on crime. It is pointed out that there is almost no evidence to show that criminality, as such, could be affected by sterilization.

There is a short chapter on genius and eugenics, wherein it is pointed out that had a program of sterilization been carried out several centuries ago, much talent would have been lost to the world; a formidable list of the names of great men with insane relatives is given in proof of this.

The concluding chapter consists of the recommendations of the committee. These, unfortunately, cannot be given in detail. It is agreed that voluntary sterilization alone should be considered in the few conditions in which a hereditary tendency exists. The committee does not believe that sterilization of normal persons can have any place in preventing the production of diseased individuals except in a few rare instances. It is recommended that one or several boards consisting of persons who have had special training and experience in the problems involved carry out sterilization procedures and that adequate legal protection be given them.

The diseases for which selective voluntary sterilization of affected persons is recommended by the committee are as follows: (1) Huntington's chorea, hereditary atrophy of the optic nerve, familial Friedreich's ataxia and certain other disabling diseases recognized to be hereditary; (2) feeblemindedness of the familial type; (3) dementia praecox; (4) manic-depressive psychosis, and (5) epilepsy, when known to be hereditary. It is stated, however, that in most of these diseases sterilization can have but little effect on the occurrence of the conditions in generations to come. The committee recommends that further research be carried out on large sections of the population to determine the "psychiatric constitution" of the community. It is recommended that a permanent committee be appointed to organize research in these directions.

The committee stresses the important fact that in a large measure no great or radical change in the complexion of society can result from a sterilization program such as the one recommended. The committee concludes that "there is no social or biological emergency which need hurry us into a widespread sterilization program based on fear and propaganda."

Each chapter in the book is well summarized in a paragraph or two at the end, and this will enable the lay reader to grasp the conclusions without going through the statistical material from which the conclusions were drawn. A complete bibliography is appended.

The Adrenals. By Arthur Grollman. Price, $5.00. Pp. 410. Baltimore : Williams & Wilkins Company, 1936.

Few authors today would have the courage to attempt a book on the adrenal glands, as the subject is in a constant state of flux and in spots is highly contro-

versial. New observations are being made with startling rapidity, and time must elapse to enable them to be verified and evaluated. The author surmounts these difficulties by dismissing or ignoring much with which he does not agree. After one has read the book there is left a decided impression that the work contains a little too much of what Grollman thinks about the adrenal glands and not enough of what others have thought and are still thinking about them. In other words, unless one is fully acquainted with this phase of endocrinology too much confidence should not be placed in many of his statements or interpretations of facts. For example, Grollman dismisses the fact that by the administration of a properly balanced mixture of electrolytes, adrenalectomized animals can be kept alive indefinitely with adrenal cortex extract, by attributing other workers' success along this line to incomplete adrenalectomy or to the presence of adrenal rests. To be sure, considerable skill is required in keeping such animals alive, but it can be done and has been done by men whose ability to perform complete adrenalectomy or to discover adrenal rests cannot be questioned. (Allers, W. D., and Kendall, E. C.: The Influence of Diet and Mineral Metabolism on Dogs After Suprarenalectomy, Proc. Staff Meet., Mayo Clin. **10**:406-409 [June 26] 1935; Am. J. Physiol., to be published. Harrop, G. A.; Soffer, L. J.; Nicholson, W. A., and Strauss, Margaret: Studies on the Suprarenal Cortex: IV. The Effect of Sodium Salts in Sustaining the Suprarenalectomized Dog, J. Exper. Med. **61**:839-860 [June 1] 1935.) Unfortunately, at the time the book was written the discoveries concerning the important relationship of potassium in the diet to the disturbance in physiology which accompanies adrenal insufficiency had not been published. Had the book been written later, a statement such as the following might not have been made on pages 193 and 194:

"The claim that administration of salts or Ringer's solution, admixed with the food or in lieu of the animal's supply of drinking water, permits the indefinite survival of adrenalectomized rats has not been confirmed by the author nor by other observers. The apparent indefinite survival and normal growth of animals on a replacement therapy consisting solely of inorganic salts must be attributed to incomplete adrenalectomy."

The foregoing remarks exemplify only one of a number of such faults. Equally disparaging comments can be made about the author's interpretation of the part played by the kidneys in adrenal insufficiency, methods of preparation and standardization of the adrenal cortex hormone and so forth.

In spite of a number of such shortcomings the book has considerable merit. It covers the territory fairly completely, and the references given are representative and about as complete as one could expect. In addition to a detailed account of most of the work done on the adrenal cortex, there are chapters on the gross and the microscopic anatomy of the adrenal glands, the chemistry, physiology and pharmacology of epinephrine and the relationship of the adrenal glands to other endocrine organs, toxins, infections, immunity and surgical shock. Much of this material cannot be found in any other one printed work on the subject, and on this account alone the book will be of considerable use to any one interested in this phase of medicine. The section devoted to clinical considerations is fairly complete, but it is suggested that any one who wishes to treat diseases of the adrenal glands would do better to consult the original works, references to which are given. In this connection it is only fair to state that Grollman makes no claims to extensive clinical experience in the treatment of diseases of the adrenal glands. Considerable space is devoted to the author's opinions concerning the cause of the symptoms which occur in the adrenogenital syndrome. It will be recalled that this syndrome is found chiefly in cases of adrenocortical tumor of women and is characterized largely by hirsutism, amenorrhea, hypertension and other symptoms very similar, if not identical, to those that occur in pituitary basophilism, as described by Harvey Cushing. Grollman attributes these symptoms to the proliferation and persistent activity of the so-called border, or "x," zone of the adrenal cortex, which in human beings normally disappears in the first year of life. For this particular zone of tissue Grollman has introduced the term "androgenic tissue." As a hypothesis, his interpretation is at least as satisfactory, if not more so, than any hypothesis which has been advanced to explain the

curious changes which occur in this disease. Furthermore, his hypothesis suggests a new line of approach to the studies of these tumors, and it is to be hoped that further histopathologic studies and experimental work will be forthcoming shortly along these lines.

Tissue Immunity. By Reuben L. Kahn, M.S., D.Sc. Price, $7.50. Pp. 726, with 54 charts, 107 tables, 7 illustrations, 2 plates in color. Springfield, Ill., Charles C. Thomas, Publisher, 1936.

The author feels that the response of fixed tissues to antigenic stimuli has not received the attention it deserves in comparison with the amount of study that has been devoted to phagocytes and circulating antibodies. He has therefore injected antigens into various tissues—most commonly the skin—of rabbits and observed the inflammatory response, the anchoring and destruction of antigen, the local necrosis and sometimes the effect on circulating antibody. Horse serum was the antigen usually employed. The immunity of tissues to bacterial or other toxins received no detailed study.

In the experimental demonstration of the importance of tissues in the response to antigens, the technologic approach is varied in many ways, and numerous features of the response are topics of discussion in the first sixteen chapters of the book. It is obviously impracticable even to list these topics here. Each chapter contains a summary and, excepting the first, a section dealing with clinical considerations. The two final chapters are devoted to "theoretical and practical aspects of tissue immunity." The numerous tables and graphs are of exceptionally consistent intelligibility.

The clinician; the pathologist; the bacteriologist; the teacher and student of immunology; the specialists in dermatology, pediatrics and allergy, and the biologist, to all of whom this book has been recommended, should be warned that the experimental work has been confined exclusively to rabbits and that the results and interpretations have been transmuted into clinical considerations on evidence that is not altogether convincing.

The quantitative aspect of these studies is emphasized, yet in many instances there is a tenfold (1,000 per cent) difference between successive amounts in the titrations recorded; in the measurement of precipitin the notoriously inferior antigen dilution method is exclusively employed. Furthermore, horse serum is a mixture of antigens, and accurate quantification of the corresponding mixture of antibodies is difficult. In many kinds of experiments the results of simple direct tests certainly cannot be interpreted with confidence.

It is to be hoped that one of the "new views" given clinical consideration on page 262 will not mislead the clinician into a potentially dangerous experiment: "The fact that large quantities of antigen can be injected intravenously in immunized animals without indications of shock is of interest in connection with practical therapeutics. It may be that the same patients who respond with local inflammation to an injection of antitoxin into a tissue [positive cutaneous reaction?], due to previous immunization with horse serum, may show no untoward effect to the injection of the antitoxin intravenously. The size of the dose is evidently important. It is the small dose that is likely to produce shock while the large dose, at least in rabbits, is less likely to produce shock."

The accounts of the experiments often are repetitious. The book could easily be condensed to a considerable extent without sacrifice of clarity or content.

Medical Classics, Volume 1, Number 1. Compiled by Emerson C. Kelley, M.D. Price, $10 per year. Pp. 78, with 9 illustrations. Baltimore: Williams & Wilkins Company, 1936.

This is a new venture; it is not a journal in the ordinary sense, though it is to be published periodically, and, on the other hand, scarcely a book, though this first number in permanent binding would materially embellish the shelves of any library.

As stated in its preface, "Medical Classics" aims to awaken the interest of all medical workers in the historical side of their profession. This first number deals

with Sir James Paget, that shrewd Victorian, who said, "To be brief is to be wise; to be epigrammatic is to be clever," and who eventually became one of the leading surgeons of his time.

There is a reproduction of the Millais portrait which gives a sufficiently good idea of Paget's appearance at the height of his career. A short biographic sketch traces his development from 1834, when, at the age of 20 and a student at St. Bartholomew's Hospital, he described Trichina spiralis, until his death in 1899. Then follow his bibliography and a little paragraph called "Eponyms," which gives references to his articles originally describing Paget's abscess, Paget's disease of the bone, Paget's disease of the nipple, Paget's tumor and Paget's mixture of mercury and potassium iodide.

Best of all, however, is the reprinting of what most authorities regard as Paget's three medical classics, entitled "On a Form of Chronic Inflammation of Bones (Osteitis Deformans)," "Additional Cases of Osteitis Deformans" and "On Disease of the Mammary Areola Preceding Cancer of the Mammary Gland." Each of these reprints is accompanied with a reproduction of the first page of the original article that is revivified, and the first reprint includes also a reproduction of the illustrations which accompanied the paper.

"Medical Classics" aims to be useful and not merely ornamental. No student can read volume 1, number 1, without feeling a sense of gratitude at being so pleasantly introduced to a great doctor who wrote perfect medical English. All teachers interested in the historical method of education will be equally pleased with the new publication, because "Medical Classics" gives promise of opening many doors that too often are securely barred. In future numbers it is planned to reproduce other medical classics that in their original form are to be found in comparatively few libraries that are easily accessible to hungry-minded beginners. Certainly the compiler of "Medical Classics" is to be warmly congratulated; may his efforts be crowned with all the success they deserve!

The Lung. By William Snow Miller, M.D., Sc.D. Emeritus Professor of Anatomy, University of Wisconsin. Price, $7.50. Pp. 209, with 152 illustrations. Springfield, Ill.: Charles C. Thomas, Publisher, 1937.

In a day of prolific publication, when so many books and articles show evidence of immaturity and seem to be largely activated by a desire to "get into print," it is a bit startling and very comforting to encounter a book that is the result of almost half a century of study and deliberation. Even if Dr. Miller had never before published even a single article, this book would make him the foremost authority of the day on the anatomy of the lung.

The book is divided into twelve chapters, in which are gathered together the results of the author's investigations on the lung, its blood vessels, its lymphatic system and its nerves. A chapter is devoted to the pleura and another chapter to a historical sketch of the development of anatomic knowledge from the time of Vesalius to the present. In all controversial situations the author states his position and defends it.

The book is profusely illustrated with cuts of excellent quality. These include photographs, photomicrographs, reconstructions and schematic drawings. Many are in color.

The book is uniformly excellent, and it is difficult to single out any portion of it for special mention. The section on the lymphatic system of the lung, pleura and bronchus gives evidence of the painstaking way in which the work was carried out, although the same attention to detail is shown in all sections.

The book is especially recommended for a place in the reference library, where it should prove extremely valuable, both for its contents and for its bibliography.

In the preface the author expresses his gratitude to a group of friends who made this publication possible. Attention should be directed also to another group of friends and a host of admirers who will affectionately treasure this book, apart from its scientific worth, simply because it was written by Dr. Miller. One of the characteristics of a truly great man is his ability to retain the love and affection of his friends and students, regardless of the eminence he attains.

Verhandlungen der deutschen Gesellschaft für Kreislaufforschung. IX Tagung. Edited by E. B. Koch, M.D., Bad Nauheim. Paper. Price, 15 marks. Pp. 378, with numerous illustrations, tables and graphs. Dresden: Theodor Steinkopff, 1936.

This volume reports the proceedings of the 1936 meeting of the *Deutsche Gesellschaft für Kreislaufforschung,* which last April was held at Bad Nauheim. The meeting lasted for three days, and the program included thirty-eight papers.

The meeting began with a presidential address. Then there followed a series of papers which, if delivered as they are printed, must have varied considerably in length; and finally many of these papers were discussed in a competent and interesting manner.

Naturally, as one might judge from the name of the society, the program centered around vascular disease, and it is interesting to realize from what a variety of angles such a general topic was discussed. There was a good deal of statistical data presented which dealt with the increasing importance of vascular disease in Germany. Then there were papers dealing with vascular insults caused by various poisons, by trauma or by electricity. Evidently in Germany, just as in this country, there is at the moment considerable interest in peripheral vascular disease, for this subject received a good deal of attention. There were also papers dealing with other baffling problems, like the relationship of occupation to arterial degeneration and the surgical treatment of hypertension. Finally, there was a group of papers dealing with cardiovascular physiology, and new methods were presented for studying and recording pulse waves and heart sounds.

The volume, as a whole, contains a good many excellent papers, which no doubt are available in other periodicals. One of the chief interests of the book lies in the fact that it covers, more or less in summary form, a wide range of subjects and gives one a chance to perceive at a glance how many of the aspects of cardiovascular disease are today being studied in several different German clinics.

The Physiology and Pharmacology of the Pituitary Body. By H. B. Van Dyke, M.D., Professor of Pharmacology, Peiping Union Medical College. Price, $4.50. Pp. 594, with 55 illustrations. Chicago: University of Chicago Press, 1936.

The author states that he has written this volume in an attempt to give an adequately documented account of the experimental work on the pituitary body during the past fifteen years, and in this he has included such clinical work as has appeared to contribute to the knowledge of this subject. The book is clearly written, well printed and well illustrated.

The difficulty of the task which the author set for himself is well marked off by his statement that in accomplishing it more than five thousand reports were consulted. Incidentally, about three thousand of these are cited in the bibliography which appears at the end of the volume.

Any book might deserve praise which was written in a conscientious effort to clear up the present chaotic state of knowledge regarding the pituitary gland and which gave a fair and critical analysis of the literature dealing with hormones and antihormones of this peculiar body. This book deserves particularly high commendation not only because it has been put together in a scholarly fashion but because it is a good deal more than an accurate and sincere bibliographic compilation. The conflicts in opinion of various observers are clearly set forth and made to coincide as far as possible, so that one feels a sense of progress in knowledge. The writing is good, so that the book is alive and interesting. Inevitably it will prove of great usefulness to all students, investigators and clinicians who have any interest in modern endocrinology.